EXHIBIT A

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE
MDL NO. 2875

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION :

THIS DOCUMENT RELATES TO Gaston Roberts et al. v. Zhejiang Huahai Pharmaceutical Co., et al., :

Case No. 1:20-cv-00946-RMB-SAK:

Videotaped remote deposition of NADIM MAHMUD, M.D., taken in the above-entitled matter before Suzanne J. Stotz, a Certified Court Reporter (License No. 30XI00184500) and Notary Public of the State of New Jersey, taken on Friday, May 2, 2025, commencing at 9:03 a.m. EDT.

APPEARANCES:

(Via videoconference)
NIGH, GOLDENBERG, RASO & VAUGHN, PLLC
BY: DANIEL A. NIGH, ESQ.
BY: C. BRETT VAUGHN, ESQ.
BY: KATHRYN AVILA, ESQ.
BY: STEPHANIE IKEN, ESQ.
14 Ridge Square NW, Third Floor
Washington, D.C. 20016
(202) 792-7927
dnigh@nighgoldenberg.com
bvaughn@nighgoldenberg.com
avila@nighgoldenberg.com
siken@nighgoldenberg.com
Attorneys for the Plaintiffs

(Via videoconference)
KIRKLAND & ELLIS LLP
BY: NINA R. ROSE, P.C.
1301 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
(202) 389-3394
nina.rose@kirkland.com
Attorneys for the Defendants

ALSO PRESENT:

William David Geigert, Videographer

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Exhibit 18	Author manuscript entitled, "Hepatocellular Carcinoma Tumor Volume Doubling Time: A Systemic Review and Meta-analysis," by Piyush Nathan, et al.	404

(Exhibits attached to transcript.)

THE VIDEOGRAPHER: Good morning. We are now on the record. My name is Bill Geigert. I'm a videographer for Golkow, a Veritext Division. Today's date is May 2nd, 2025, and the time is 9:03 a.m.

This remote video deposition is being held in the matter of Valsartan, Losartan, and Irbesartan Products Liability Litigation. The deponent is Dr. Nadim Mahmud.

All parties to this deposition are appearing remotely and have agreed to the witness being sworn in remotely.

Due to the nature of remote reporting, please pause briefly before speaking to ensure all parties are heard completely.

All counsel will be noted on the stenographic record.

The court reporter is Suzanne Stotz, and she will now swear in the witness.

THE COURT REPORTER: Could you raise your hand.

THE WITNESS: (Complies with request.)

N A D I M M A H M U D, M. D., having first been duly sworn, was examined and testified as follows:

THE COURT REPORTER: Thank you. You may proceed.

EXAMINATION

BY MR. VAUGHN:

Q. Hello, Doctor.

Am I saying your name right, Dr. Mahmud?

A. Yes. You've got it, Counselor.

Q. Awesome have you ever been deposed before?

A. No. This is my first time.

Q. Have you ever served as an expert witness before?

A. No, I have not.

Q. Okay. I want to run through just some of the basic rules. I'm sure Ms. Rose went over them with you.

We'll do our best not to talk over each other. I'll ask you a question. Wait a few seconds so Nina can launch an objection if she wants before you respond. I will do my

best to let you fully respond before I ask my next question. Sometimes with, you know, video or if we get too conversational, we might talk over each other. So let's try not to do that. If we do, the court reporter will let us know so we can stop so she can get a good record. I'll try to not talk too fast so she can get a good record; I have a tendency to. So she'll let us know if either of us are talking too fast.

If I ask any questions that you don't understand, you can just ask me to ask it again or to rephrase. Does that make sense?

A. Yes. That makes sense.

Q. And when you're answering questions let's try and do a yes, no or something that's not a head nod just so that she can transcribe it. Does that make sense?

A. Yes, it does.

Q. And if you answer a question, we are going to assume that you understood the question. Does that make sense?

A. Yes, that's fair.

Q. And then I typically take breaks about every hour or so. I drink quite a bit of

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coffee while I'm going.
If you ever need a break, though, just let me know. As long as we're not, like, mid-document or, like, midline of, questioning, we'll take a break or find the quickest break that we can take. Okay?
A. Sure. That sounds good.
Q. Did you bring any notes with you today?
A. Only my expert report and Dr. Siddiqui's expert report.
Q. Do you have those printed off?
A. I have them on my computer, not printed physically.
Q. Okay. So is there any typed notes that go along with it or just the report?
A. Just the reports.
Q. Do you have any programs open on your computer other than Zoom and whatever you're using to view the reports?
A. I have my Outlook inbox open, but I'm happy to close that if necessary.
Q. Yeah. If you don't mind closing that and no messaging with anyone outside while we're doing the depo.

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A. Yeah. Okay, that's closed.
Q. Is anyone else with you currently in the room?
A. No. Just me.
Q. And I don't want to know any communications you've had with attorneys, any of the substance, but did you prepare with attorneys prior to this deposition?
A. Yeah. I met with counsel to review aspects of what a deposition is and what to expect and some logistics.
Q. How many times did you meet with counsel?
A. Throughout the entire course of my involvement in the case or just leading up to the deposition?
Q. Leading up to the deposition?
A. Perhaps on three occasions.
Q. And approximately how many total hours?
A. If I have to approximate, maybe on the order of perhaps four hours.
Q. And who all was present at those meetings?
A. My recollection -- so it varied depending on the meeting. There was different counsel that attended different meetings, so Ms. Rose was present, Mr. Trangle, Ms. Davidson I believe is her last name. Those are the three that I recall.

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Q. And prior to being retained for this litigation, were you familiar with the substance N-Nitrosodimethylamine, which is abbreviated NDMA?
A. Yes, I was familiar with generally what nitrosamines are. We -- during the course of medical education we learn a little bit about nitrosamines. I wasn't intimately familiar with, you know, literature related to NDMA-contaminated Valsartan specifically in any detail.
Q. Were you familiar with NDMA specifically prior to this litigation?
A. Yes.
Q. And what was your understanding of NDMA prior to this litigation?
A. So NDMA, again, is mostly familiarity from medical school. We learn about different nitrosamines, NDMA, other nitrosamines as well, mostly in the context of dietary exposures from my recollection. It was many years ago. But that's I think when I was first introduced to what NDMA is.

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Q. And what does class do you think you would have been in that introduced you to NDMA?
A. I believe it would have been biochemistry or biochemistry as applicable to medicine type of course. It's one of the first year courses we take in medical school.
Q. And did you have any courses after that first year of medical school --
MS. ROSE: Object to the form.
BY MR. VAUGHN:
Q. -- in NDMA?
A. It's hard to recall specifically. I don't think -- my recollection is we learned about it in this kind of principles of biochemistry type of class. I couldn't say concretely if we encountered NDMA again in our secondary classes. The program I went to at Stanford we moved relatively quickly into clinics, so there was a lot of clinical exposure. So most of our didactic electro-based content is in the first year.

Q. Did you guys review studies of NDMA while you were in medical school?
A. It's likely that they showed us some animal literature. That class in particular is very basic science focused, talking about, you know, molecular pathways, enzymatic pathways, things of that nature. And so I think in that context, you know, I expect they showed us some basic science literature from animal studies.
Q. And what was the purpose of learning about NDMA in medical school?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. I think, you know, broadly speaking, you know, they try to educate us about a wide range of metabolic pathways, enzymatic pathways, and ways in which different substances, different exposures can interact with these metabolic pathways. Oftentimes there is a heavy focus on enzymatic mechanisms and specific proteins or enzymes that are relevant in different types of pathways. And so I think that that was likely introduced in that

context.
BY MR. VAUGHN:
Q. And do you recall what metabolic pathways NDMA interacts with in a human or in animals?
A. So, again, I don't recall any specific human data that they might have shared wit us. Again, this is now well more than a decade ago, so it's hard to recall specifics of what they may have shown us, but it, you know, is likely related to carcinogenesis in animals.
Q. Did they tell you in medical school NDMA was likely carcinogenic in humans?
A. I don't recall hearing that specifically, no.
Q. And you were in medical school to treat humans, not in veterinarian school to treat animals, right?
MS. ROSE: Object to the form.
THE WITNESS: That's true that obviously our primary focus in medical school is ultimately to learn to treat humans, but we are also educated broadly about the scientific literature and where our understanding of molecular mechanisms,

drug development, things like this that requires a broad knowledge base of, you know, some degree of basic science literature as well.
So, yes, I mean obviously I'm not treating animals in my practice, but it's relevant to learn about broad principles of animal research that may or may not be relevant to humans, depending on the particulars of the research question and the study.
BY MR. VAUGHN:
Q. In school your teacher was presenting those to you as NDMA, the metabolic pathways in animals, did they think that was relevant for how it might impact humans?
MS. ROSE: Object to the form.
THE WITNESS: I'm not certain. I don't recall, you know -- I don't recall that professor positing anything specific about that. I think that professor I think actually was -- I don't think he was a clinician. I believe he was Ph.D. basic scientist, from my recollection, so he's very focused on the basic science aspects

of this, not so much that's really direct clinical translation.
BY MR. VAUGHN:
Q. And do you recall how long this course was where they were talking about NDMA? Was it a single day or was this like for the entire semester they were discussing NDMA?
A. It was certainly not the entire semester. I think we covered a wide range of subjects related to biochemistry and biophysics were relevant. So I don't know, it might have been maybe two lectures at most, but I suspect it was probably just a single lecture and not even an entire lecture dedicated to this. It was probably discussed in the context of other exposures and other pathways as well, though, again, I can't recall with any real detail because it was -- this was back in like 2008, 2009, so it was a long time ago.
Q. So most of what you have learned about NDMA was through this litigation?
A. I think much -- yeah. So I think in this litigation, certainly as applied to NDMA-contaminated Valsartan, yeah, this is the first time I looked in real detail carefully at

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a lot of the literature from animal studies and human studies. This doesn't really come up in the course of my routine care as a hepatologist really at all. I've never had to posit that NDMA could have been plausibly linked to any liver related outcome in my practice. So, yes, I would say that the deep dive into the literature with respect to the specific question in this case was done in the context of this case.

THE COURT REPORTER: I'm sorry, Doctor, if you could slow down a little bit, I would appreciate it. Thank you.

THE WITNESS: My apologies.

BY MR. VAUGHN:

Q. Approximately what year do you believe you were in medical school when you were going over NDMA?

A. I think I stated it to be the year 2008 to 2009. That would have been my first year of medical school at Stanford.

Q. And you submitted an expert report in this litigation, correct?

A. I did, yes.

Q. We are going to drop --

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MS. ROSE: Mr. Vaughn, sorry, I am so sorry to interrupt, and I should stated it right at the beginning of the deposition, but Dr. Mahmud had a typographically correction to something in his report that he wanted to raise at the deposition.

MR. VAUGHN: I was just about to ask if he had any corrections.

MS. ROSE: Okay, well, perfect.

MR. VAUGHN: You beat me to my next question, Nina.

MS. ROSE: I'm sorry, I had forgotten to raise it at the very beginning.

THE WITNESS: I also did.

BY MR. VAUGHN:

Q. Not -- not a problem. We're going to drop that first, the report into the share file. And let me know once you can access that, and I will try and share screen it.

A. All right. I think I'm able to see it as Exhibit 1.

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(Whereupon, Exhibit 1, Expert Report of Nadim Mahmud, M.D., M.S., M.P.H., M.S.C.E., was marked for identification.)

BY MR. VAUGHN:

Q. All right. And are you able to see it also on my screen where I'm screen sharing?

A. Yes, I can.

Q. If we need it. Is it zoomed in properly or is it zoomed out really far?

A. It's somewhat zoomed out. I can see it. It's very small, but I can see it.

Q. Give me one second. Just play around with it before I get going too far. Is that better or worse?

A. It's a little better.

Q. Okay. I guess first, do you have any corrections that you would like to make to your expert report before we get going?

A. Yes. And thanks for offering the opportunity. There is one correction I'd like to make that I just found yesterday when I was just rereading my report.

Let's see, it's on page -- let me search this document. On page 21 at the very

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bottom paragraph that begins with "Fifth." So it says, "Fifth, the cross-sectional imaging performed on Mr. Roberts in April 2016 independently confirmed the presence of cirrhosis. On 4/19/2016, Ms. Roberts underwent a CT of the abdomen and pelvis. The treating radiologist's report states:" And then I have a quote there. I erroneously -- so I initially intended to pull a quote from the radiology report that's referenced further up in my expert report during the medical records reviewed portion. And I erroneously put that quote around my own interpretation. That's why it begins with "'My review of this imaging.'" I am intending that to come from me. So "'My review of this imaging demonstrates a very clear nodular contour of the liver,'" that's attributable to my own interpretation of the imaging. The quote that I intended to pull there is found on page 8 where I quote the treating radiologist report of the CT scan. And I am happy to read that into the record. So that report states, "'Peripheral margin of the liver is somewhat lobulated, particularly along the infra aspect of the left lobe.'"

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"'Although nonspecific, findings above may be evidence of liver cirrhosis.'" That is what I intended to pull down there. So my apologies for the oversight.

Q. So this part I'm highlighting is what you're talking about?

A. Yes. Specifically right after -- the quote that's given right after the treating radiology -- radiologist's report states.

Q. I'm sorry. Are you saying that this quote should be different or that the person that it is attributed to should be different?

A. I don't intend to quote that at all, actually.

Q. So you're going to strike this from your report?

MS. ROSE: I don't believe that is what the witness is saying.

THE WITNESS: I'm not saying to strike it from the report. I'm saying you can attribute what is quoted to me as the expert witness. I intended --

BY MR. VAUGHN:

Q. Okay. So -- sorry. As opposed to

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the treating radiologist's reports, it would be your opinion is and then this quote?

A. I intend to insert the treating radiologist's reports quote that is cited -- or that's given on page 8 in my report. I intended to pull that quote down, but I guess erroneously I forgot to pull the quote down and then I accidentally put the quotes around the statement attributable to me instead. Does that make sense.

Q. Which quote -- I went to page 8. Which quote is it you're saying, this one right "'The peripheral margin,'" that's what it is supposed to say?

A. Exactly. I'm supposed to be pulling that whole quote in there from "'The peripheral margin,'" including "the impression: "'Although nonspecific, findings above may be evidence of liver cirrhosis.'" That's from the treating radiologist's report. So I intended to pull that quote down to be inserted right after the colon the treating radiologist's reports states and then insert that quote. The rest of the text --

Q. And then the next sentence is your

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own? It was just this one here with the quote?

A. Yes, that's right.

Q. Okay. I understand. Thank you for that clarification.

A. Thank you.

Q. Are there any other corrections in your report?

A. No.

Q. Okay. And your purpose as an expert witness was to respond to the opinions offered by Dr. Siddiqui; is that correct?

A. Yes. My understanding is I'm offering an opinion as to specific causation expert to respond to the plaintiff medical expert witness, Dr. Siddiqui.

Q. And you understand she was a specific causation expert as well, correct?

A. Yes, I do understand that.

Q. And did you review Dr. Siddiqui's report?

A. Yes, I did.

Q. And did you review her supporting citations in the materials considered as well?

A. Yes, I did.

Q. And are you aware that we've

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already had general causation phase of this litigation?

A. Yes, I think I'm aware that there have been depositions related to general causation.

Q. Okay. And are you aware that the plaintiff's experts are allowed to testify on general causation regarding the levels of NDMA in Valsartan being able to cause liver cancer?

MS. ROSE: Object to the form.

THE WITNESS: Are you referring to specific causation experts commenting on that?

BY MR. VAUGHN:

Q. No. Are you aware that the general causation experts have been allowed by the Court to testify regarding the levels of NDMA in Valsartan being capable of causing liver cancer?

MS. ROSE: Object to the form.

THE WITNESS: I don't know if I discussed that in any great detail with counsel, but that seems reasonable that the general causation experts would talk about the general plausibility of the

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causal link that's allege in the case.
BY MR. VAUGHN:
Q. And that the Court has found they have a sufficient basis to make those opinions?
MS. ROSE: Object to the form. The doctor is not here to comment on the Court's rulings or what it means.
THE WITNESS: I am the not privy to the Court's rulings on that specific matter.
BY MR. VAUGHN:
Q. Did you see that Dr. Siddiqui reviewed the plaintiff's general causation report, such as Dr. Panigrahy, the cancer researcher?
MS. ROSE: Object to the form.
THE WITNESS: You have to show me specifically. I don't recall off the top of my head. But if that is listed in her list of reviewed materials, then I would take her word for it.
BY MR. VAUGHN:
Q. Okay. But Dr. Panigrahy's report is like 200-some pages. Do you recall if you reviewed his actual report and the basis of his

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report?
MS. ROSE: Object to the form.
THE WITNESS: Dr. Panigrahy's reports, you would have to probably show me. I can't recall specifically if I reviewed that one in detail or not.
BY MR. VAUGHN:
Q. Okay. And then your report that you wrote is 42 pages; is that correct? The signed page is on 42?
A. I think the entire document length is 70 pages.
Q. 70 pages, okay. And the rest of those are like citations and the exhibits, such as your CV?
A. Right, yes.
Q. Okay. On page 61, Exhibit B, is your materials considered list. And so these are all studies that you reviewed in forming your opinions in this case?
A. Yes. These are the articles that I believe I cite these all directly at some point in my expert report, yes, as well as the additional materials I considered.
Q. And you reviewed these materials

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considered?
A. Yes.
Q. And then you note deposition transcripts. So you reviewed these deposition transcripts as well?
A. Yeah. The deposition transcripts listed, yes, these ones I have reviewed.
Q. Okay. And then like some of these you actually cite in your report, like Dr. Hooks' deposition, correct?
A. That's correct.
Q. Did you review any of these in more detail than others?
A. I would say that some of them were more relevant to my opinions. And so there are certain sections of certain depositions that I found to be more relevant; and those are usually represented by areas that I have cited to support my opinions in the case. And then some depositions were less relevant. So, for instance, you know, a detailed deposition history from a pulmonologist is a little bit less relevant to this specific causation case.
So, yes, I mean there was variation and which depositions I found to be more or

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less informative to forming my opinions about the case.
Q. Was Dr. Hooks one that you found informative?
A. Yes. Dr. Hooks was one of the treating radiologists. And I did find both, you know, his notes and the medical record and his deposition informative.
Q. So you reviewed his deposition in detail?
A. Yes, I would say so.
Q. And then these are the expert reports that you reviewed: Dr. Mele, Siddiqui, Russo, Sawyer, and Chernyak?
A. Yes. I think the only additional thing to note would be the deposition transcript from Dr. Siddiqui from this past week which I also reviewed.
Q. And so if an expert is not listed here, you didn't review it, such as Dr. Panigrahy's?
A. That's correct. I don't recall reviewing Dr. Panigrahy's report.
Q. And then the next section is stamped records. You reviewed all these

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medical records of the plaintiff, Mr. Roberts?
A. Yes, I did.
Q. The next exhibit is going to be the invoice you produced with the Notice of Deposition -- or in response to the Notice of Deposition. Let me know once you have access to that.
A. I can see it.
Q. One second. All right.
So this invoice was on April 2nd, 2025?
A. Yes.
(Whereupon, Exhibit 2, Invoice Number INV-01, dated April 2, 2025, was marked for identification.)
BY MR. VAUGHN:
Q. All right. I see you started drafting your expert report here on 3/8/2025. Do you recall what you initially started drafting in your expert report that first day?
A. I expect I -- you know, I spent a lot of time prior to that reviewing the medical records. And so at that time I believe I was starting to really try to piece together the medical records kind of chronologically and get

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a sense of the timeline. That's where I recall starting.
Q. And at that time did you form an opinion in this case?
A. It's hard to recall exactly on that day if I had already had a formed opinion, because I felt my opinions were being formed in the course of reviewing the records. But, you know, I don't think I had solidified all of the points in my opinion at that point yet. I was still in the process of reviewing records actively, reviewing the literature actively. I was really focused on just getting a clear report of the chronology and gathering the data at that stage. So I think the opinion that, you know, was really formed over the course of many, many more hours on -- in the ensuing week or so.
Q. By the point that you had started drafting your expert report had you determined that NDMA was not a cause of Mr. Roberts' cancer?
MS. ROSE: Object to the form.
THE WITNESS: You know, I think at that point just going through the record I

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was already identifying other very significant well-established risk factors that I was very concerned were very likely to have been related directly to his hepatocellular carcinoma.
Again, I was in the process of forming an opinion about NDMA-contaminated Valsartan. And I think at point I was just beginning to engage shortly after that really was literature to review. So I don't I think I had solidified an opinion about NDMA-contaminated Valsartan's relevance to his particular case at that point.
Like I said, at that stage I was mostly getting the chronology together. And then, with my clinical background, obviously as I'm putting together chronology, I identified risk factors that I think are relevant to, for instance, cirrhosis, obesity, diabetes, so I was aware of those things in the chronology. And that wasn't forming my evolving opinion of the case.

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BY MR. VAUGHN:
Q. And so at the time you started drafting your expert report on March 8, 2025 you had not yet done any literature review on NDMA; is that correct?
MS. ROSE: Object to the form.
THE WITNESS: I may -- I believe I had looked at, you know, in some fashion some of the human studies, but not in any extreme detail to scrutinize them from a methodologic standpoint.
I think I began at least on the invoice four days later I mentioned literature review. And that's the phase where I was very actively looking through the literature and trying to understand strengths and weaknesses of studies.
So, like I said, you know, the general process which is -- which parallels I think what a clinician does, you gather information first, you gather the data about the patient, the chronology, the history so you know what salient points to look at when you are interpreting the literature. So that's my

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general process. I want to understand the facts of the case and the chronology of the case, the comorbidities, et cetera, first. And then I take that knowledge of the case to help me interpret the literature through the appropriate lens.
BY MR. VAUGHN:
Q. So you started drafting your expert report prior to evaluating that NDMA literature, correct?
MS. ROSE: Object to the form. This has been asked and answered.
THE WITNESS: So there are -- obviously my report is very long. The entire document is 70 pages. And there are aspects of the report that are not directly related to the specific medical records. I mean there is also my CV, for instance. There is my summary of my own background qualifications, that is another aspect that I think I was probably drafting early on in addition to the medical records, kind of chronological review. So those aspects of the report, you know, they don't require a detailed

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literature review at that phase. It is really when I am talking about my opinions and supporting that with evidence and literature, that is when the literature review becomes most relevant.
BY MR. VAUGHN:
Q. Ad so are you saying that you draft your report and then you find literature to support your opinions; is that correct?
MS. ROSE: Object to the form. It misstates what the witness said.
THE WITNESS: No, that is not correct. I -- as a clinician and a clinician scientist, hopefully you have seen my background, I'm a clinician scientist, I have a high standard when I review medical records and studies. I maintain an open mind and I evaluate what I view to be strengths and weaknesses of the scientific literature, interpret that in the context of a specific case.
So I went into this review with a very open mind to try evaluate the weight of evidence supporting one position and the weight of evidence supporting another

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position to make an informed opinion.
BY MR. VAUGHN:
Q. And then Dr. Siddiqui submitted her report on 3/10/2025; does that sound right?
A. I don't recall the exact date, but that sounds roughly correct.
Q. Okay. And so from that point on it looks like you billed 47 hours. Does that look approximately right or do you want to add it up?
A. It looks approximately correct. I will take your word for the math. We can just add it up, but that sounds about right.
Q. Okay. And for that 47 hours that included more review of records, the review of literature, the drafting of your expert report, and communicating with counsel; is that correct?
A. Yes.
Q. Okay. As you said, you had a 70-page expert report. So part of that 47 hours was drafting your 40 -- or your 70-page expert report, correct?
A. Yes.
Q. Approximately how many of those

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hours do you think were spent drafting your expert report, the 70-page expert report, how many of those 47 hours?
A. I would be approximating, but probably at least 20 of them.
Q. Approximately how many of those hours do you believe were communicating with counsel?
A. Well, so those would be separate. Of the 47 hours, I don't think there was very much communication with counsel during this phase. I have only listed it on one day, on the 14th. You know, I had a meeting with counsel, it was probably no more than two hours I would expect.
Q. Two hours. And out of those 47 hours, how many of those hours do you think were reviewing medical records?
A. So, let's see, I've given you 20 plus two so far, so that leaves 25 hours to account for. Yeah, so I would say the records review and literature review, a lot of that is happening in tandem as well as kind of simultaneously drafting aspects of the report. It is hard to kind of delineate very

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specifically. It is not like I sat for 20 hours and only drafted the report. I oftentimes was drafting while I am also reviewing records and literature. But I would say that, you know, probably an additional five to ten of those hours are really looking at dedicated sections of the records to double check or triple check things or identify additional important points.

Q. So five to ten hours on the medical records during that time probably?

A. Yes. Again, with the caveat that I'm often when I'm -- the hours I have given you when I'm, quote, unquote, "drafting the report," I'm likely also looking back at records as well as some literature. So a lot of these overlapping. I can't put them in boxes so cleanly.

Q. And then would you have an estimate of those 47 hours how many were spent on reviewing literature?

A. I suppose the remainder of the math. So it's 25 minus 5 to 7, so, I don't know, probably 18 to 20-ish hours.

Q. And would you consider most of that

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literature review was on the various causes of liver cancer or was most of it on researching NDMA?

MS. ROSE: Object to the form.

THE WITNESS: I was fairly comprehensive in my approach. I tried to identify really as much relevant literature to this case as possible.

So I did searches both for NDMA in both animal studies and human studies. In particular, obviously I was interested in NDMA-contaminated Valsartan studies from the human literature, which is most directly relevant to the case. But, yes. And I also reviewed in detail relevant literature that pertained to Mr. Roberts' case and his other comorbidities. So I did include a broad literature review and search of relevant risk factors in his history pertaining to developing hepatocellular carcinoma. That includes looking at major national and international hepatology society guidelines which represent standard of care, state-of-the-art best practice for

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managing these patients and thinking about these patients.

So I would say it was quite broad in terms of literature search. There were searches that were really focused on NDMA. There were searches that were really focused on literature. And I did my best to be comprehensive.

BY MR. VAUGHN:

Q. Are you aware of what cumulative dose of NDMA Mr. Roberts was exposed to?

A. Yes. I can't remember the exact number off the top of my head, but, you know, I would be happy to reference it with you.

I know in -- I recall in Dr. Sawyer's deposition he outlines it, you know, informed with the different expected ranges of contamination per Valsartan tablet, which my recollection on the high end of the estimate was around 20,000 micrograms potentially per tablet. And then, you know, if you assume with perfect adherence where he took that dose every single day for the exposure period, you know, he arrives at the cumulative dose. But I can't remember the exact number

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off the top of my head. But I would be happy to review that specific number again with you. But that is the methodology that was used to calculate the cumulative dose.

Q. Does that number appear anywhere in your expert report?

A. I don't recall putting that number in directly into the report.

Q. Did you consider that number in coming to your opinions in this case?

A. Yeah. I certainly considered his exposure, his dose exposure, and cumulative exposure. But there were many other factors in this case that made me very confident that his NDMA Valsartan-contaminated exposure was completely implausibly related to his hepatocellular carcinoma.

I focused on the arguments that I thought were really the most relevant and the strongest arguments to clearly articulate that case. And so it was not the most relevant piece to actually add up and calculate his cumulative dose exposure. And nor am I toxicologist. I'm a clinician. He is really trying to assess specific causality in this

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case and be responsive to Dr. Siddiqui's expert report. You know, we don't routinely calculate cumulative dose exposures in this fashion for most patients, except in perhaps very unusual cases. So I looked at it through that lens in my capacity as a clinician and a clinician scientist; not a toxicologist.

Q. So you are not a toxicologist, correct?

A. Correct, I am not a toxicologist.

Q. And you are not giving any toxicology opinions in this case, correct?

A. No, I am not offering any opinions as a toxicologist because I am not one. I may have some opinions that may be in some way related to toxicology, again, with my perspective as a clinician primarily.

Q. Have you investigated what dose of NDMA it would take to give a human liver cancer?

MS. ROSE: Object to the form.

THE WITNESS: So my review of the human literature is that it's very much not at all well-established that NDMA is even plausibly capable of causing

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hepatocellular carcinoma specifically in humans. A lot of this is imputed from the animal literature. And so I do have a sense from the animal literature of what doses of NDMA were given and observed to be linked with different types of cancers, including liver cancers. And very briefly they're extremely high doses that are used in general in animal studies, usually on the scale of milligrams per kilogram per day, which are orders of magnitude higher than what is studied or observed in these epidemiologic studies in humans.

So to that extent, there is no real human data that very clearly scientifically in a way it's well-established links NDMA in humans specifically to hepatocellular carcinoma. So it's hard to make a statement about what dose could potentially do that.

But if you try to impute from the animal literature, animals require extremely high doses relative to what's been studied in humans to observe those effects.

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BY MR. VAUGHN:

Q. And, therefore, you don't believe there is any plausible capability of NDMA causing liver cancer in humans?

MS. ROSE: Object to the form.

THE WITNESS: I have not seen any high quality scientific evidence specifically in humans that NDMA-contaminated Valsartan can cause hepatocellular carcinoma specifically in humans. So I reserve the right to revise that opinion if there is a new study that comes out that's very well conducted that accounts for potential biases and confounders and limitations to demonstrate from a causal inference standpoint that it is causally linked to HCC, yeah, I would reserve my right to revise the opinion if a new study comes out.

But based on the literature I found and reviewed, including that which has been cited by Dr. Siddiqui, I don't find any compelling well-established evidence to show that at the doses that have been studied that there is any well-established

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link with hepatocellular carcinoma in humans.

BY MR. VAUGHN:

Q. Did you look at any higher doses? So outside of Valsartan, just NDMA in general, do you have any opinions on what dose it would take to cause liver damage?

MS. ROSE: Object to the form.

THE WITNESS: Yes. As I said, most of the -- the highest quality evidence for NDMA in carcinogenesis really comes from well controlled experimental settings in animals where the doses that are being used are at a completely different order of magnitude than routine dietary exposures that humans have or even environmental exposures or certainly pharmaceutical level exposures, there are orders of magnitude different. So I am not comfortable as a clinician and a clinician science translating directly from an animal study, you know, in a very different setting in a totally different model, you know, rodents versus humans, for instance, you really cannot take a

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one-to-one translation from an animal study to a human study. So I rely on the human studies to make those ascertainments of what is expected to be observed in humans.

The summary I have given you is basically that I don't find any compelling evidence to really demonstrate that link in humans.

BY MR. VAUGHN:

Q. And because you are a clinician, not a toxicologist, you don't do that dose conversion from animals to humans, correct?

MS. ROSE: Object to the form.

THE WITNESS: Like I said, I am not a toxicologist. But as a clinician, I do understand principles of dosing medications. So I do prescribe medications and, you know, I do dose medications appropriately for humans. So I understand principles of doses in concentrations. So that's something that I think any clinician should understand.

So there is certain aspects of toxicology that obviously I am not an

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expert on and wouldn't claim to be an expert on, but I do understand concentrations.

And so milligrams per kilogram, which is a very commonly used way of thinking about a concentration of something, you can look at what those doses are in animals and compare them to humans. And that is relevant, because obviously, you know, animals, like rodents, are obviously very different in size to humans, so it is relevant to know how many milligrams or nanograms or micrograms per kilogram are given to an animal. It is actually an additional limitation of the human studies that there is no accounting for weight in human patients.

So like if you -- just as a brief example, if you look at the FDA's threshold limit of 96 nanograms per day of NDMA, they don't account for kilograms, they don't account for body weight of individuals; but any clinician ought to know that if you give a certain dose of

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something to someone who weighs 250 pounds, there is a different expected effect than if you gave the same absolute dose to someone who weighs 120 pounds.

So those principles I understand as a clinician in terms of dosing, you know, milligrams or whatever per weight. Those principles are important and I think are translatable to some extent between animal and human studies.

BY MR. VAUGHN:

Q. In your opinion is NDMA a mutagen?

A. In my opinion in animal studies NDMA has been plausibly linked to being mutagenic, yes, for DNA in animals.

Q. What do you mean by plausibly linked?

A. I find the evidence from animal studies to be scientifically sound. And, again, I am not a basic scientist myself; but, you know, they have explored some of the potential mechanisms in the basic science literature to understand how it could plausibly lead to DNA damage in mutations. For instance, there is literature that demonstrates that NDMA

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in the basic science setting can act as an alkylating agent for DNA which can lead to DNA mutations. So I accept that in the basic science animal literature NDMA does have this very plausible mechanistic explanation for how it could lead to DNA damage.

Q. Can those DNA damage and mutations then lead to cancer in those animals?

A. Yeah, I do think that that's plausible. And, you know, the scenario of that I think in Dr. Sawyer's deposition -- I'm sorry, his expert report, from my recollection, he does go over some of the mechanisms of how NDMA in the animal basic science setting could act as an initiator and as a promoter in the carcinogenesis pathway. And I think that there is likely sufficient evidence in the animal literature to show that in that particular setting NDMA could -- you know, does have a mechanistic basis for leading to cancer in animals in those basic science animal studies.

Q. Do you believe that NDMA does not cause DNA mutations in humans?

MS. ROSE: Object to the form.

THE WITNESS: So, again, my

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opinions on that in humans are informed by the literature. And it's not as simple of a question of binary does DNA cause this, yes or no. You have to consider things like doses. Many things can potentially have a toxic effect if you give a sufficiently high dose; but at much lower doses or routinely environmentally exposed doses it may not have that toxic effect. So there is more nuance.

I mean even something as simple as water, if you were to ask me if water can be toxic, if you drink enough of it, yes, it can be toxic, it can kill you.

So it's -- you have to, in my view, really think about the details, not just the binary yes or no does this cause this. It's the details of the exposure, the dose of the exposure, the duration of the exposure, the latency, the biological plausibility of the mechanisms, you have to consider all of these things together when you are making an assessment of whether a particular exposure like NDMA or a particular patient, based on their

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context, could have plausibly led to a cancer like hepatocellular carcinoma.

THE COURT REPORTER: I'm sorry, Doctor, if I could remind you to slow down a little bit.

THE WITNESS: I apologize.

BY MR. VAUGHN:

Q. How much water does a human have to consume to kill them?

A. Quite a bit. You would have to drink quite a bit of water. I mean I can't recall like off the top of my head exactly how much it might take; but many, many, many liters of water consumed over a relatively short period of time would lead to low sodium levels that could cause basically, you know, neurological issues that could lead to someone's death. But it can happen. I mean it's observed to happen. Individuals do die from this that have issued where they have some sort of mental -- I'm sorry, cognitive pathology that leads them to consume tremendous amounts of water. So that does happen. But I can't tell you exactly how many liters to take; it varies from individual to individual based

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on who they are. But, yeah, I suspect that if a drank ten liters of water today I might get very sick and need to be hospitalized.

Q. In your research you did for this case, did you come across the case studies of humans dying from NDMA ingestion?

MS. ROSE: Object to the form.

THE WITNESS: I did come across case studies where, you know, an individual in a case report, for instance, was allegedly exposed to NDMA and then later, you know, they died and there was an autopsy done. And, for instance, I recall one specific case report where on the autopsy the patient had cirrhosis and it had some plausible NDMA exposure. So, yes, I do recall coming case studies of that nature, if that's what you're referring to.

BY MR. VAUGHN:

Q. What do you mean by plausible NDMA exposure? Do you remember how they were exposed?

A. You would have to show me which specific case report you are thinking of.

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The one that I'm trying to recall is there may have been an occupational exposure to some nitrosamine. I don't remember the specific context, but I think there was a case report I remember seeing that there is some environmental exposure where the individual was exposed to NDMA and likely other exposures as well in sort of an industrial kind of setting. So that's why I say plausible, because it is not likely to be one specific exposure. There is probably myriad toxins in those settings someone might be exposed to. But I do recall a case report of that nature where on the autopsy they looked at the liver and there was cirrhosis. I remember a case report like that.

Q. Have you seen any case studies where someone has intentionally poisoned someone else with NDMA and killed them?

A. It's possible I came across that, but I don't recall that specifically off the top of my head.

Q. Do you know at what level NDMA has been shown to be lethal to humans?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. So I -- like I

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said, I rely on the scientific literature to inform my opinions about the potential of something like NDMA to potentially, you know, in a scientific valid way, cause an adverse outcome in a human.

And, generally speaking, case series and case reports are not a valid way scientifically to establish risk factors. By definition those are descriptives -- broadly speaking, like in terms of types of studies there are, there are descriptive studies, there are analytic studies. Descriptive studies do not attempt to draw an association statistically between any exposure and an outcome; they just report what happens.

And why that's so relevant is -- for instance, you can't estimate a relative risk from a case series or a case report. You need to perform an analytical study. So some observational study or interventional study like a randomized trial.

I really I'm speaking fast so I'll slow down again.

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But that's very important because we have a kind of a pyramid of quality of evidence; and case series and case reports are at the very bottom of the totem pole. No scientist will really rely on that to adjudicate a risk factor.

So if somebody in a case report was given a high dose of NDMA and then died, I don't know for a fact that that individual died because of the NDMA. They may have had other comorbid conditions or something else that resulted in them dying and it is just a correlation. So that's why you need analytic studies to study individuals who have an exposure and compare them to individuals who don't have the exposure and then account for different types of the confounders to minimize bias to make a very specific association between a potential exposure and an outcome. That's where I kind of rank those case series and case reports when I review literature.

BY MR. VAUGHN:

Q. And so you're saying you would need a randomized trial on NDMA in humans before we can conclude that it causes cancer in humans?

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MS. ROSE: Object to the form. It misstates the witness.

THE WITNESS: No, I did not say that. I do not think that -- so I don't think it would be ethical necessarily to -- it would not be ethical to perform a randomized control trial where you give individuals NDMA and randomize them to exposed or unexposed. But you can perform very high quality observational studies using methodology that's very well thought out that can support causal inference.

I know this from my background as a clinician scientist. I'm a clinical epidemiologist and so those are the types of studies that I perform. I perform observational epidemiologic studies, including, from epidemiologic studies, which can provide very strong evidence if they are well conducted and they account for important biases.

So, no, I don't think the standard of evidence would require a randomized trial. I don't think we would ever have a

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randomized trial to demonstrate toxicity of NDMA in humans. That would not be ethical based on the animal literature. If you see a signal in the animal literature that something may have the potential to be carcinogenic in humans, we wouldn't be able to ethically randomize patients to NDMA or not. And that's true of many, you know, potential exposures that, you know, might have a potential harm in humans whether or not they actually do. So that is an ethical principle that's commonly applied in randomized controlled trials.

BY MR. VAUGHN:

Q. So it would be unethical to give humans NDMA at the dose that Mr. Roberts was taking, correct?

MS. ROSE: Object to the form.

THE WITNESS: So I think, if I just kind of read the question properly, if this was a randomized trial -- so Mr. Roberts' exposure was quite different; it's from a contaminated pharmaceutical. Like a randomized trial would be done in

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an interventional setting where someone is given just NDMA as an exposure versus a placebo. But, in general, probably at, you know, any dose above the FDA threshold it would be unethical to randomize someone to that daily exposure versus not.

BY MR. VAUGHN:

Q. And what is the FDA's reasonably safe threshold?

MS. ROSE: Object to the form.

THE WITNESS: My recollection of their threshold is 96 nanograms per day. But there is a lot of context around that, that the FDA provides in their own industry guidance.

It's -- so the FDA guidance very importantly is 96 nanograms per day over a 70-year human lifespan. And they arrive at that threshold imputing a very wide margin of safety from the animal literature to be very conservative, which is I understand to be a typical FDA practice. They want to offer a very conservative wide margin of safety. But they translate from the animal studies to

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a 70-year lifespan of a human. And they arrive at the 96 nanograms per day of daily exposure for 70 years. That would translate to 1 additional cancer per 100,000 individuals with that exposure.

I provide that context here because I think it's directly relevant to Mr. Roberts' case, because obviously he didn't have a lifetime of exposure, he had less than two years of exposure to NDMA. So it doesn't really match the FDA's assumptions that go into, you know, toxic exposures, which they understand to be -- have a very long latency period, which is why they scale this over an entire human lifespan of 70 years.

But that's my understanding of the FDA threshold to answer your question.

BY MR. VAUGHN:

Q. Do you agree with the FDA's calculation?

A. So, you know, as a clinician, I'm not a drug regulator, I don't work for the FDA, I don't, you know, independently verify their calculations. I assume that folks in the FDA

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are careful to do this, but, like I said, I understand the general principles of what they do. They look at the animal literature and see what dose the animals may potentially be harmful in humans and then they add a huge layer of margin of safety, because 1 additional a cancer per 100,000 in my view is very, very conservative. When you compare it to the magnitude of risk factors in Mr. Roberts' case where, you know, there is like a 2 percent -- 2 to 4 percent annual instance of hepatocellular carcinoma in patients with cirrhosis, they are in completely different universes of risk. So that's just to give you an illustration of how conservative the FDA is.

But, to your question, I didn't independently verify what animal study they chose to use to do the math to translate that to this very conservative risk scale for humans, but I have no reason to doubt that they would do that with good scrutiny and rigor.

Q. You said the 96 nanograms that the FDA set, did you do the math to see how many nanograms that would be over a lifetime? You talked about this is over 70 years. Do you

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know what cumulative lifetime dose would be of 96 nanograms?

A. I did do the math, actually, when I was thinking about this. I can't recall the number off the top of my head, but I did do the calculation. It's in the millions of nanograms of lifetime exposure over 70 years. Yes, I did do that.

Q. Which is a high exposure, right, millions of nanograms?

MS. ROSE: Object to the form.

THE WITNESS: I mean it's a large number. I mean whether or not you consider it to be a high exposure, it is still small relative to doses that were used in animal studies. It is still orders of magnitudes smaller than what is used in the animal literature, but yes. So nanograms, obviously there are orders of magnitudes smaller than the milligrams. And, like I said, the animal studies, they are typically dosing animals on the order, you know, in the milligrams scale of concentration. So nanograms is ten to the negative ninth. Milligrams is ten to the

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negative third. So they are orders of magnitude different, but that's the math. I mean that's the math the FDA arrives at it is in the range of millions of nanograms over a lifetime.

BY MR. VAUGHN:

Q. And do you recall Mr. Roberts' cumulative exposure to NDMA?

MS. ROSE: Object to the form.

THE WITNESS: I do recall his exposure. Like I said before, I think he is the high end. So if we take the most conservative estimate and assume that he had the maximal possible exposure, which, again, is very conservative from the plaintiff's perspective, that would give him 20,000 micrograms -- I'm sorry, 20,000 nanograms per day. 20,000 nanograms per day of exposure.

And when I was thinking about the FDA's cumulative lifetime exposure, I did calculate Mr. Roberts' Cumulative exposure over his shorter window of time, because obviously he was getting a daily exposure above the FDA's threshold limit. And his

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lifetime exposure was higher than the FDA's threshold lifetime limit. And when I did the math -- and, again, I would have to -- we could independently do the calculations again if necessary, but off the top of my head my recollection was he was exposed over his window of time to somewhere in the ballpark of 5 to 6 times above the lifetime threshold of the FDA's limit. That's my recollection.

Q. And so the FDA's lifetime limit, Mr. Roberts was exposed to several times higher than that in just a two-year period?

A. Yes.

MS. ROSE: Object to the form.

THE WITNESS: I'm sorry.

Yes. Again, assume, taking the assumptions, all the conservative assumptions, which are likely not to be true, it is unlikely that he truly was getting the maximal NDMA exposure with every single pill and it is unlikely that he was -- we don't even know if he was adherent to taking a pill every day. But if I am taking, again, the most

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conservative scenario where I will just -- to take -- to argue the side that he got the maximal exposure for the hypothetical, if he did, in fact, get a high dose every single day for as long as he was prescribed Valsartan, he would have had, from my calculations, probably a five- to six-fold higher exposure than the lifetime exposure limit from the FDA.

And the reason why I gave all the context of how he arrives at that is what that would mean for him is he would have had over a lifetime, if there were 100,000 people just like Mr. Roberts who had that exposure spread out over a lifetime, 5 to 6 of them out of that 100,000 might have developed a liver cancer if we accept hypothetically that there is a well-established link. And, again, my position is that there is not a well-established link demonstrated, but that is me being as charitable as possible to the plaintiff position is at most he would have had, you know, 5 to 6 out of 100,000 risk of developing an HCC.

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That's setting aside all the issues of temporality and latency, which I think are bigger problems honestly. It's completely implausible to develop a hepatocellular carcinoma over the time course that Mr. Roberts was exposed.

But on the dosing question specifically, that's what I would say.

BY MR. VAUGHN:

Q. And so you think because he had 5 to 6 times the dose of what the FDA says is a lifetime dose and he had that dose in a two-year period, you think it is just a 5 times higher risk of 5 out of 100,000 or 6 out of 100,000; is that your opinion?

MS. ROSE: Object to the form.

THE WITNESS: So just to clarify, you know, I would be translating that -- I mean for a one-to-one comparison to the FDA's lifetime limit you have to assume a lifetime of chronic exposure for Mr. Roberts as well, which, as you said, he did not have. He had a much more concentrated shorter window exposure.

So I'm just giving you the numbers

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if he had had that exposure spread out over 70 years you would expect that his risk of developing a cancer, if we were to accept that there is a true causal link, which, again, I don't accept for humans, would be 5 to 6 out of 100,000.

I think it's -- my position is that when you additionally account for the fact that he had a very short concentrated exposure, it's even less plausible for him to have developed a hepatocellular carcinoma, because toxic exposures causing solid tumors there is typically a very long latency. It's usually many, many, many years or decades before somebody would develop a solid tumor from any toxic exposure. That I think is actually an extremely important point in this case, that he started NDMA and then over a relatively short period of time was then formally diagnosed with hepatocellular carcinoma.

The carcinogenesis sequence that I alluded to previously, induction, promotion, aggression, that Dr. Sawyer

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also mentions -- and he really doesn't talk about latency of those periods, unfortunately -- there is a very long latency between these steps. It takes a long time for a healthy cell to acquire mutations that then lead to carcinogenesis; it's typically decades.

So that's I think an additional problematic element to try to make a causal association in this specific case.

BY MR. VAUGHN:

Q. Is your opinion based more on the latency than the carcinogenicity of NDMA?

MS. ROSE: Object to the form.

THE WITNESS: No. So when I make my opinion I try to weigh all the relevant factors. I'm highlighting -- you know, because you're asking about the dosing of the Valsartan, I'm highlighting aspects of my opinion that are relevant when thinking about that particular question. But there are other elements of my opinion that are equally, if not more, relevant to my opinion that NDMA-contaminated Valsartan was really not relevant to Mr. Roberts'

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hepatocellular carcinoma.

So it is really one of many points, but I'm putting emphasis on it now because that is the area that we are talking about.

BY MR. VAUGHN:

Q. In the human -- do you think the human body is able to repair the DNA damage that NDMA causes?

MS. ROSE: Object to the form.

THE WITNESS: So, again, I don't accept that there is -- I don't accept that there is really well-founded literature to demonstrate carcinogenicity of NDMA specifically in humans. But with that caveat, if I were to hypothetically assume that NDMA could do that, the punitive mechanism in animals is that it's -- that toxic metabolites from NDMA can lead to DNA damage through things like alkylation of the DNA and things like that.

Cells are equipped with mechanisms to repair DNA. There are DNA repair mechanisms, yes. So cells can do this.

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That's why it's not a guarantee that a cell that has DNA damage, it's not a guarantee that that cell will eventually turn into a cancer. We have many safeguards in our cells and DNA repair mechanisms to prevent that from happening. It's really only when someone is exposed to very chronically to a carcinogen that provides the right environmental milieu around those types of cells that have acquired DNA damage that they will acquire more DNA damage and mutations over time that serve as precursors to potential cancer down the line.

And that is an articulation -- it's important to articulate that demonstrates why it's such a slow process. I can't think of any specific toxic exposure that could plausibly cause hepatocellular carcinoma over such a short window. Even the most toxic exposures that I am aware of in my practice as a hepatologist, like aflatoxin or extremely high-dose radiation, the latency period between initial injury and chronic exposure and

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hepatocellular carcinoma on the shortest time scale is probably five to ten years.

So, yes, I mean, we are equipped with mechanisms in our cells to repair this damage. And it requires very, very chronic long-term exposure to -- you know, repeated chronic exposure to a carcinogen to cause these changes that result in a cancer.

MS. ROSE: Mr. Vaughn, we've been going for about an hour. Are you at a good place for a break?

If you are in the middle of something, we can certainly keep going for a little bit; but I wanted to raise that.

MR. VAUGHN: You're good. Let me ask one question.

BY MR. VAUGHN:

Q. Cancer aside, I just want to talk about liver damage real quick, is it your opinion that NDMA cannot cause liver damage in humans?

MS. ROSE: Object to the form.

THE WITNESS: Yes. So I think my opinion is that there is no well-founded

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scientific literature that demonstrate that NDMA-contaminated Valsartan certainly, there is nothing that really definitely links that in humans with respect to liver damage, no. I think that comes from primarily the animal literature.

BY MR. VAUGHN:

Q. Sorry. Just a moment.

Setting the Valsartan aside, just NDMA, is it your opinion that NDMA itself cannot cause liver damage in humans?

A. Yeah. I mean, I haven't come across any, like I said, high quality scientific evidence that would demonstrate that NDMA specifically, with or without Valsartan, induces liver injury in humans.

I think -- if I'm understanding your question correctly, there is other literature about NDMA primarily from like dietary exposures where they look at an association between dietary NDMA and different types of outcomes, including liver-related outcomes. But I don't find those to be extremely compelling for reasons I'm happy to

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talk about in the future if you want to.

But -- you know, but dietary studies are oftentimes fraught with lots of different biases, and I don't find them independently to be, you know, strong scientific evidence of a causal link between NDMA and liver cancer or, you know, liver cirrhosis, no.

MR. VAUGHN: Okay. Now's a good time for a break, Nina.

MS. ROSE: Great.

THE VIDEOGRAPHER: Off the record at 10:10 a.m.

(Whereupon, a break was taken.)

THE VIDEOGRAPHER: We are back on the record at 10:24 a.m.

BY MR. VAUGHN:

Q. Hello, Doctor.

A. Hello.

Q. You're a gastroenterologist, correct?

A. Yes, I am a gastroenterologist, but also a transplant hepatologist.

Q. So you are a hepatologist as well, correct?

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A. Correct.

Q. Okay. And in practice is that what you're doing is transplant hepatology?

A. Yes. That's my primary practice.

Q. And you are not an oncologist, correct?

A. Correct, I'm not an oncologist.

Q. Do you diagnose cancer?

A. Yes.

Q. And is that once they come to you or -- in what setting are you diagnosing cancer?

A. So in my clinical practice as a transplant hepatologist.

Just very briefly to give you the context of what that means. I take care of patients who have chronic liver disease across the entire spectrum of their liver disease. So individuals who don't have cirrhosis but have chronic liver disease, individuals who have cirrhosis, who have compensated cirrhosis, decompensated cirrhosis, who may require a liver transplant; and I take care of them in the post-transplant setting if they require transplant.

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I diagnose cancers in the course of my routine care of my patients because every patient with cirrhosis, we have to screen them for liver cancer. So I am the one who is ordering their cancer screening studies, ultrasounds, alpha-fetoprotein, CT scans, MRIs if necessary. I am the one who is following up on those images to -- to determine if there's something concerning or not who's then doing the additional work-up.

And then I -- I work at a transplant center, so I participate in multidisciplinary tumor boards. So if I find something on an MRI that's concerning for liver cancer in a patient with cirrhosis, I will -- I will bring that case to our multidisciplinary tumor board to review it with the radiologist, the surgeons, other hepatologists, and medical oncologists who take care of these patients to confirm the diagnosis, make a treatment plan.

These things are usually done in a multidisciplinary setting, but I am the primary, you know, provider that is responsible for screening for it and then diagnosing the cancer, hepatocellular carcinoma, and other

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liver cancers in these patients.

Q. Does there have to be a confirmation diagnosis when you make a diagnosis of cancer?

A. I'm not entirely sure as to what you mean by "confirmation diagnosis." Maybe you could clarify.

Q. You said you take it to a -- when you diagnose someone with cancer, you take it to a multidisciplinary board; and then a medical oncologist confirms the diagnosis.

Is that always the case, that someone else is going to confirm your cancer diagnosis?

MS. ROSE: Object to the form. Misstates the witness's testimony.

THE WITNESS: No. I wouldn't summarize it that way. Maybe I can clarify. I order the studies that would di- -- would be relevant to diagnose a potential hepatocellular carcinoma, for instance. And I will look at the images myself.

Let's say that if there's a patient that needs an MRI and there is a mass

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there, I will look at the MRI. I will kind of make my own assessment of, you know, is this concerning for hepatocellular carcinoma or not.

But, of course, I will rely on the diagnostic radiologist's read. And usually the diagnostic radiologist will be able to make a very clear assessment of the likelihood that this is, in fact, hepatocellular carcinoma by applying the LI-RADS criteria, and that is usually sufficient.

If -- if there's a LI-RADS 5 lesion, which is basically -- that's regarding to be diagnostic of hepatocellular carcinoma, that diagnosis, I -- I would already been aware of when I bring the case to the tumor board.

So the tumor board, sure, we're all confirming that as a board, we agree that there's hepatocellular carcinoma; but I'm not relying on the hemato-oncologists, for instance, to make the diagnosis.

The diagnosis is usually made if it's a LI-RADS 5. It's more about

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thinking about the next steps, what -- the best way to treat the patient; and that requires multidisciplinary discussion.

I would say that there are also more borderline cases, like if it's a LI-RADS 3 or a LI-RADS 4, that is not independently diagnostic of hepatocellular carcinoma. And so we -- we still may review those images in the tumor board just to agree upon a surveillance strategy, for instance.

BY MR. VAUGHN:

Q. And if you think there's cancer and someone on the tumor board says that there's not cancer, such as the oncologist, which opinion trumps?

A. So in that instance where there's disagreement about whether or not a cancer is present, that might arise, let's say, in -- it's a pretty rare circumstance.

Most of the time, I think, we're a little bit differential to the diagnostic radiologist who has the most expertise in interpreting the cross-sectional images because it's -- it's their dedicated expertise.

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So if the radiologist is very confident that something is a LI-RADS 5, we -- we accept that as the tumor board, you know, that it's LI-RADS 5 lesion.

I can't think of a case where, like, the medical oncologist is, you know, disagreeing with the diagnostic radiology expert about LI-RADS 5 lesion, but there are maybe some scenarios where it might be a LI-RADS 4 and we have a discussion as a group about, you know, what is the urgency to try to confirm that this is or is not hepatocellular carcinoma.

And so in that scenario, if there's disagreement, we may pursue biopsy to get further -- to really kind of get, as a gold standard, confirmation of the presence or absence of cancer.

Q. And you said you're not a radiologist, but you do review the actual imaging, correct?

A. Yes.

Q. And in practice if the diagnostic radiologist disagreed with you, you would defer to them?

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MS. ROSE: Object to the form.

THE WITNESS: It would really depend on the nature of the disagreement. I mean, there have been scenarios where, you know, the initial diagnostic read that's reported, when I look at the imaging, I might identify something that I am concerned about that I think might have been missed in the radiology report; and then I'll have a discussion with the radiologist.

And I can recall a couple of scenarios where I've identified something that I think was missed, and then I bring it to the radiologist. They re-review it and say, oh, okay, yes. Actually, in retrospect, this does appear to be the case; and they might amend their report.

That does happen on occasion, but it's usually if there's a disagreement. Or if I'm concerned about something, I'll just have a conversation with them; and we'll review it together.

But overall, yes. I -- I -- at the end of the day, I primarily trust our

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diagnostic radiologists at -- at my institution. I think they're very good, and they have much more dedicated expertise in reviewing radiology than I do. They do it day in and day out as their job.

So -- so yes. I mean, if they feel strongly that -- that their read is accurate and they can show me why, then yes, I'll -- I'll agree with -- with what their opinion is.

BY MR. VAUGHN:

Q. Do you agree that the oncologists have more expertise than you do in diagnosing cancer?

A. So that's a very broad statement. I mean, if I were just narrow that down to hepatocellular carcinoma specifically, I would not uniformly agree with that because, like I said, the oncologists are usually not the ones who are making the diagnosis. They're not the ones who are screening these patients for cancer.

The on- -- medical oncologists in the setting of hepatocellular carcinoma are

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most often involved with more advanced late-stage cancers because the medical oncologists will be involved in administering immunotherapy or sometimes systemic chemotherapy, things along those lines that are really treatments more for patients who have very advanced disease.

So in the setting specifically for hepatocellular carcinoma, medical oncologists are oftentimes involved very late in the process, and they're -- they're usually not -- they don't have a whole lot of primacy in the diagnosis. And the screening of hepatocellular carcinoma, that's usually the role of the hepatologist.

Q. And is that because liver cancer is typically caught at earlier stages?

MS. ROSE: Object to the form.

THE WITNESS: We tried to -- sorry.

MS. ROSE: Go ahead, Doctor.

THE WITNESS: Apologies.

Ideally, we identify patients that require screening. So any patient with cirrhosis, for instance, should enter a surveillance pipeline for getting imaging

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and blood work every six months.
And the intention of that is to identify liver cancers early so that we can treat it more effectively and hopefully cure it. Obviously there are patients where, for -- for one reason or another, they're not identified as having cirrhosis or they don't complete their surveillance appropriately, and then cancers may get diagnosed at a later stage; but our -- our aspiration is to try to catch them early.
BY MR. VAUGHN:
Q. From the time that there's cirrhosis, how quickly can that turn to HCC?
A. So based on the established literature, you know, and, you know, national and international hepatology society guidelines, our best estimates are that there's an annual risk of somewhere in the range of 1 to 8 percent depending on the specific cohort or etiology of liver disease you're looking at. It's -- it's somewhere in that range.
I think Dr. Siddiqui in her report acknowledged 2 to 4 percent annual incidence of

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HCC in those patients, which I generally agree with. It's somewhere in that ballpark.
Q. And so you're talking annual incidence, and my question's a little different.
From the first time that they have cirrhosis, how quickly can that cirrhosis turn to HCC?
A. So it's -- it's hard to -- it's -- I mean, it -- there are many patients who are diagnosed simultaneously with cirrhosis and HCC. I can really only frame it to you in terms of annual risk.
You know, 2 to 4 percent of patients will develop a liver cancer within a year of having cirrhosis. So it can happen relatively quickly. It can happen on the time course of a year, but it varies depending on the patient, the -- the cause of the liver disease, and based on some type factors that we don't fully understand. But I can tell you that that's the rate.
And because of that, we screen all patients with cirrhosis for liver cancer because they all have a very high risk of

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developing a liver cancer even within one year.
So -- but they -- cancers, they have different rates of growth. There's some variation how fast a tumor can grow and thus be detectable. I mean, sometimes you might have a microscopic cancer that we don't see on imaging, but it might be there; but it takes some time for it to grow to the point where it's actually observable microscopically on an ultrasound or an MRI. But that's the best way I can kind of frame the answer.
Q. Do you have an opinion on if cirrhosis to go to HCC within six months?
MS. ROSE: Object to the form.
THE WITNESS: So as I stated, I mean, there are many patients that are simultaneously diagnosed with cirrhosis and HCC, and I do think that a patient with cirrhosis that's -- let's say a patient's diagnosed with cirrhosis. Could they have an HCC six months later? Absolutely.
And the reason I say that is because it's possible to have an HCC even in the absence of cirrhosis, especially in

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patients who have MASLD and MASH. It's very well demonstrated in the literature that -- that patients have a real risk of developing an HCC even before their degreeing -- their degree of scarring has progressed to cirrhosis.
BY MR. VAUGHN:
Q. And so the diagnosis of HCC wouldn't actually support that someone has cirrhosis alone, correct?
A. There's a very high likelihood that the patient will -- will -- would have cirrhosis. I think somewhere in the ballpark of 80 percent of patients who have an HCC have underlying cirrhosis; but no, it's not a guarantee that if the only you looked at was the HCC, it ' not a guarantee that they have cirrhosis, no.
Q. So you can't say, hey, this person has HCC, therefore, they have cirrhosis, correct?
A. No, you can't say that. You'd have to look at -- you'd have to do an assessment to see if they actually have cirrhosis or not.
Q. And how do you do that assessment?

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A. It's a good question. So there -- there's -- there are a lot of factors that come into consideration; but broadly speaking, there are imaging features that we look for. There are features on blood work. There are prediction scores that we calculate from blood work and patient age.

And sometimes if there's really advanced cirrhosis, you would may expect certain clinical symptoms or clinical signs; but usually it's a composite of these different data points.

You try to assimilate some laboratory prediction modeling data points and imaging data points to come to an assessment.

Q. So you would agree it's not imaging alone that you diagnose cirrhosis?

MS. ROSE: Object to the form.

THE WITNESS: Sorry.

MS. ROSE: Go ahead. Sorry.

THE WITNESS: I wouldn't agree with it quite in that fashion because in some patients you -- you really can't make the diagnosis.

I mean, so, for instance, if you

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were to see, you know, multiple high probability features on a CT scan that are -- that are, you know, that come with cirrhosis, you can generally make that diagnosis.

But let's say that you only saw one suggested imaging feature of cirrhosis. I personally don't rely on that alone. I -- I would look also to laboratory findings and -- and laboratory-based prediction models to add another data point to try to make the assessment.

BY MR. VAUGHN:

Q. And what labs are you looking for to make that assessment of cirrhosis?

A. So --

MS. ROSE: Object to the form.

THE WITNESS: So again, you know, I never rely -- I try not to rely exclusively necessarily on -- on labs. It's usually a composite of different data points.

There -- there can be some patients that have really overt obvious signs of cirrhosis based on blood work alone where

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it really pushes me in the direction of cirrhosis; but generally speaking, I'm looking at labs, including the AST, the ALT, the platelet count. I'm looking at the patient age.

Those -- those four things together are used to compute prediction score called the FIB-4 score or the fibrosis-4 score, which is it's codified in our guidelines that this is a -- a screening tool that we use in patients to stratify individuals into different probabilities of risk of having significant scar in the liver, advanced fibrosis or cirrhosis, or -- or essentially, you know, minimal scar in the liver or something in between.

So we compute that for all patients, you know, that have, you know, chronic liver disease, such as MASLD or MASH as an initial assessment; but those are some important labs.

Other labs that I look at that are important are so-called liver synthetic function markers. So in addition to platelet count, that's also albumin. It's

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also INR that are important liver synthetic function markers, and bilirubin.

BY MR. VAUGHN:

Q. Why are those three important -- albumin, INR, and bilirubin -- when it comes to liver function?

A. So your liver has a lot of important roles in your body. My view, it's the most important organ as a biased hepatologist.

But one of the -- among the things it does is it's a -- it's a major manufacturing hub for proteins in your body as well as clotting factors.

So albumin is the -- is the major protein in the body. It's the most predominant protein in -- in the body, and it's manufactured in the liver.

So if your liver has cirrhosis and a lot of scar, the liver does not function well; and so it's not able to produce albumin as much. And so in a patient with very advanced cirrhosis, we might start to see the albumin come down gradually because the liver's not functioning well to produce it.

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A sim- -- a similar principle applies INR, which is a clotting factor marker. It's a measure of kind of production of clotting factors. Some -- some, but not all, clotting factors are produced in the liver. So if there's cirrhosis, as it gets more advanced, the INR may become abnormal.

And the directionality's different. The INR actually goes up as -- as cirrhosis worsens over time; whereas, the albumin goes down. But that's usually the general significance.

The bilirubin tends to become elevated usually only in very, very late stages of cirrhosis, really advanced decompensated cirrhosis most of the time.

Q. And so would you agree that typically if the albumin and INR and bilirubin are normal, the patient does not have advanced cirrhosis?

MS. ROSE: Object to the form.

THE WITNESS: I would not uniformly agree to that. There's a lot of nuance that goes into interpreting these labs.

I would say in general, patients

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with advanced decompensated cirrhosis, you do expect to see progressive derangements in those labs. But the issue is that those labs can be altered for other issues oftentimes unrelated to liver disease.

So you have to interpret all -- all of this in the context of the particular patient.

But the general trends I articulated to you are things you see as cirrhosis becomes more advanced; but it's important to highlight that even if those are normal, it does not rule out the presence of cirrhosis.

BY MR. VAUGHN:

Q. Would it rule out the presence of advanced cirrhosis?

A. Not necessarily. I -- I wouldn't say that either. So for instance, it's very common for patients to be on a blood thinner, and the blood thinner can make the INR abnormal. And so we then can't rely on the INR as a marker of synthetic function.

Likewise, some of the albumin reduction that can happen over time in

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cirrhosis, that can, to some extent, be overcome with very aggressive nutritional supplementation.

So -- so like I said, there's nuance in interpreting these things, and you have to interpret it in a particular patient context.

Q. You were talking about if it was abnormal. I'm talking about if all of those are normal.

If all of those labs are normal, does that mean they do not have advanced cirrhosis?

A. If they're all normal and, in particular, like, looking the trends, like, I don't like to rely on, like, an isolated lab trend because sometimes there can be temporary or acute changes that cause things to fluctuate; but I would say it makes it less likely. I would agree it makes it less likely. If those things are all normal, it's less likely that the patient would have very, very advanced cirrhosis, yes.

Q. And did you review the labs, albumin, INR, and bilirubin in Mr. Roberts'

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case.

A. I did. But I should emphasize one other thing that -- you know, the other important lab that I think you're leaving out is platelet count. And that's actually also another one of these synthetic function markers that's -- that's very critical to highlight as well.

So that's -- I would throw that in the bucket of important labs to assess when you're looking at progression of liver disease and cirrhosis.

So yes, I did review these labs for Mr. Roberts, including his, you know, transaminases, his FIB-4 over time, and his platelet count over time.

Q. But for advanced cirrhosis, you 'e looking at more at the albumin, INR, and bilirubin, correct?

MS. ROSE: Object to the form.

THE WITNESS: No. I'm looking at the composite of these labs, and I'm -- I'm also very carefully looking at the platelet count. The platelet count is actually a very, very important marker of

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progression of cirrhosis between stages -- between stages of compensated and decompensated cirrhosis.

The platelet count is a very, very important marker of something called portal hypertension. It's elevated pressures kind of, you know, behind the liver in the large vein that's flowing into the liver.

And the full hypertension -- the blood pressure in this portal system begins to climb as patient's severity of cirrhosis increases. And the platelet count will begin to decrease gradually as that gets worse.

So that is oftentimes a very early indicator that a patient's progressing to more advanced cirrhosis.

BY MR. VAUGHN:

Q. How low of a platelet count would you anticipate for advanced cirrhosis?

MS. ROSE: Object to the form.

THE WITNESS: There's a lot of variability in patients, so I can't give you, like, a -- a concrete cutpoint

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because oftentimes you're looking at the trend.

I'll say as a general marker, a platelet count of less than 150 is regarded to be abnormal. That's abnormally low. That's the definition of thrombocytopenia, which just means low platelet count. But the trend is important.

So I mean, if someone's baseline is 300 and it's been 300 for years and years and then over the past year, I see it's gone down from 300 to 250 to 200 to 155, that ' a concerning trend even though it's still technically above this threshold of less than 150.

If a platelet count used to be normal and is now less than 150, that's very concerning to me in a patient that I'm worried about cirrhosis.

BY MR. VAUGHN:

Q. Would you consider the platelets one of the most important lab findings for Mr. Roberts in coming to your conclusions?

A. Yes, it's a very important lab

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finding.

Q. And why is that in Mr. Roberts' case?

A. I'd say there's -- there are -- are two important contributors of the platelet count that come to mind in his case. One, it's a component in that FIB-4 calculation. I forget if I gave you the whole formula, but it -- it involves the AST, the ALT, the platelet counts, and the age. So all of those components go into an assessment of the likelihood of cirrhosis. So that that hopefully articulates why the platelet count is an independent important marker of the likelihood of cirrhosis.

But in reviewing Mr. Roberts records, you know, his platelet count used to be normal; and then it gradually began to decline.

I'm sorry. I'm pulling up my report to just look at the timeline in case that becomes relevant. But off the top of my head, I remember very specifically his, I think, primary care physician Dr. Sanders. He noted on -- on multiple occasions and during

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their visits that the platelet count had become low, and he did not understand why. But that it used to be normal.

So Dr. Sanders had identified that as an unusual finding which I think with the benefit of me being able to look at the entire record, I recognize that is clearly an indicator that Mr. Roberts had developed cirrhosis that was becoming more advanced. But that's why it was very relevant.

He used to have normal platelet count, and then it trended down during the course of his medical course, which I viewed to be consistent with his diagnosis of cirrhosis.

Q. You say you were looking at the timeline on this.

What was the first date that he was actually diagnosed with thrombocytopenia?

A. I'm sorry. Let me just pull up my report. Sorry. Bear with me. I've got my medical timeline here up now. All right.

I did try to note down in my review of his record where I saw platelet counts and tried to note that where it was relevant.

So let's see. In 2009 it was 174,

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so it was not in the range that I would say is thrombocytopenia at that time. In -- okay. So in November, November 4th, 2015, his platelet count was 137. That is thrombocytopenia.

Q. Was he --

A. That is abnormally low.

Q. Was he diagnosed with thrombocytopenia at that point?

A. The -- the definition of thrombocytopenia is the lab value. So I don't know if any particular physician directly said -- you know, I don't know if any of his treating physicians articulated it at that time, but that value is the definition of thrombocytopenia. He had thrombocytopenia on that date at that time.

Q. Are you a hematologist?

A. I'm not a hematologist.

Q. Do you order labs?

A. I order labs all the time, yes.

Q. Do you read labs?

A. I read labs all the time.

Q. How do you know if the labs are out of range?

A. Well, so it's -- generally a normal

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range is reported by -- by a particular lab, and that may vary based on the particular lab where it's obtained.

However, there are well-established thresholds in the field of liver disease specifically where there are benchmark values that signify abnormalities that may differ from laboratory-reported reference ranges. That includes things like AST, ALT, and platelet count.

So any hepatologist will tell you that thrombocytopenia is less than 150 because it's codified in our guidelines. We make decisions from hepatology international and national guidelines that actually use that threshold of the platelet count of less than 150.

So I always interpret that in that context where a lab may have a reference range, which may vary from lab to lab; but I have numbers that I understand to be abnormal from my perspective as a hepatologist.

Q. Have you ever worked in one of these labs that sets reference ranges?

A. No. I mean, I -- I've never worked

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in -- in a laboratory that runs, you know, these -- these tests myself, no.

Q. Do you know how they set their reference ranges?

A. I have an understanding for -- it may vary by -- from lab to lab, but I have a general sense of how these are set. And I actually know this specifically for things like transaminases because understanding the methodology for that comes from is an important lesson for why us as hepatologists have our own set of understood normal versus abnormal ranges.

So just I'll be very concise. AST and ALT, there are normal ranges that are very commonly reported. Let's say ALT. You might see a lab that says, you know, up to an ALT of 39 might be normal. To a hepatologist an ALT of 39 is abnormal.

The reason why it's -- why we -- we have -- why we say this is when they determine reference ranges for transaminases, oftentimes these were -- were -- were done by taking individuals from the population that were taught to be healthy. They measured their

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labs. You get a bell curve. You get a bell distribution for what the range of labs are, and you can look at, you know, the 95th percentiles on either side. You get a range of where 95 percent of the data fall.

And then it could be beyond that, you know. I'm not saying it's always specifically 95 percent, but they use this principle to determine what is kind of an outline value above or below the normal range for a general population.

That's oftentimes how these things are set, but that's important to understand because where a lot of the reference ranges came from for ALT and AST, individuals who were thought to be healthy, many of them had underlying chronic liver disease, including things like Hepatitis C that was not yet diagnosed.

So many of the individuals who were used for this calculation from a normal healthy population, in fact, had underlying liver disease that was unrecognized. So the normal values are skewed from reference ranges at labs to the upside.

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It's really kind of more -- more recent literature that demonstrates that if you really isolate the truly healthy patients who don't have any evidence of chronic liver disease, you get a much lower upper limit of the lower value.

But yeah. That's my general understanding of how these things are oftentimes developed or reported, but it may vary from lab to lab; and I'm not privy to, you know, how Labcorp or Quest may do it. They may do it differently.

Q. And so you're not aware if there's different sensitivities in the labs that different companies do?

A. Sorry. What do you mean by "sensitivity" in that context?

Q. Things that could make the results different based on how they are doing the test, and so they might have difference reference ranges based on that.

Are you aware of that?

MS. ROSE: Object to the form.

THE WITNESS: You know, like I said, I -- I don't work in, you know, in

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the industry of -- of, you know, kind of running and adjudicating these labs ranges. So I'm not privy to how one lab may do this versus the other one.

All I can say is that I understand that reference ranges vary across different labs, but that we have very specific important thresholds when we are applying lab results to patients with liver disease.

BY MR. VAUGHN:

Q. Okay. You testified earlier you wouldn't want to rely on just one lab but lab trends.

In your practice have you observed different results from one lab to another --

MS. ROSE: Object to the form.

BY MR. VAUGHN:

Q. -- on the same patient?

A. Not generally. I mean, I -- there are different lab ranges; but, you know, I do have patients -- for instance, I take care of veterans, and they -- they'll get labs done at the VA sometimes, and sometimes they'll get labs done outside at Labcorp or --

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You know, the absolute numbers are generally consistent, I would say. It would be unusual if I see really outliners all through one lab relative to another one. It's usually more the reference range, in my experience, that might be reported as being slightly different.

Q. You work at Penn Medicine, right?

A. Yes.

Q. Okay. I'm going to share the screen.

This is your profile on their website, correct?

A. Yes.

Q. And it has here your expertise, and it lists many things.

It doesn't actually list HCC, does it?

A. It lists liver cancer --

Q. Okay.

A. -- in the bottom right.

MS. ROSE: Mr. Vaughn, I'm sorry. Is this introduced as an exhibit?

MR. VAUGHN: No.

MS. ROSE: Oh, you're showing him

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something that you're not introducing as an exhibit so we can't see the full --

MR. VAUGHN: I can scroll. I'll go through it. I thought you did this just the other day with Siddiqui when you were deposing her.

MS. ROSE: No, I didn't. I introduced -- everything I showed her I was introduced as an exhibit. I didn't put anything on the screen, actually.

MR. VAUGHN: Oh, okay. Well, if you want me to take a break and print screen it and make it an exhibit, I will.

MS. ROSE: I think anything that's shown to the witness and discussed should be introduced as an exhibit. So that --

MR. VAUGHN: Okay.

MS. ROSE: -- for the benefit of the record, we understand what you're pointing to and what's stated on the document.

MR. VAUGHN: All right. Let's take a break.

MS. ROSE: Okay. Thanks.

THE VIDEOGRAPHER: We're off the

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record at 10:56.
(Whereupon, a break was taken.)
THE VIDEOGRAPHER: We are back on the record at 11:03 a.m.
BY MR. VAUGHN:
Q. All right. Doctor, sorry about that.
A. That's okay. No problem.
Q. All right. So I have that web page now as an exhibit. This will be Exhibit 3. It should also be dropped if you need to look at it as the full exhibit.
(Whereupon, Exhibit 3, PennMedicine.org profile of Nadim Mahmud, MD, MS, MPH, MSCE, was marked for identification.)
BY MR. VAUGHN:
Q. And all right. And earlier I was talking about where it says "liver cancer."
And so it doesn't say HCC, but you agree that liver cancer is essentially synonymous with HCC?
MS. ROSE: Object to the form.
THE WITNESS: I would say that HCC is a type of liver cancer. My expertise

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in liver cancer extends beyond the HCC. It includes other types of liver cancers. For example, bile duct cancers like cholangiocarcinoma.
BY MR. VAUGHN:
Q. And so then cirrhosis is not listed on here, is it?
A. I'm looking through here. It's -- liver failure I think, you know, is encompassing, you know, aspects of, you know, the progression of chronic liver disease to -- to, you know, up to and including cirrhosis.
Q. Okay.
A. And I'm sorry to interrupt. But -- and also, you know, while the word "cirrhosis" may not be literally written out here, all of the -- you know, many of the relevant liver diseases are detailed here for expertise, like, alcoholic liver disease, autoimmune hepatitis, Hepatitis C, et cetera. These are all things that cause chronic liver disease and cirrhosis.
So that I use that as a clarifying point.
Q. And so this lists many things that can cause cirrhosis?

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A. Yeah. This lists many things that cause cirrhosis. And It also lists many complications of cirrhosis, you know, for instance, things like ascites, esophageal varices, liver cancer, as well, you know, the relevant therapies that are used for cirrhosis like liver transplantation. I believe those are all listed here.
Q. You know that cirrhosis can cause liver cancer.
Can it go the other way as well?
Can liver cancer cause cirrhosis?
A. No. No. HCC does not cause cirrhosis.
Q. And why is that?
A. So essentially, cirrhosis is a state where there is a significant amount of scarring, you know, typically throughout the liver that results from chronic inflammation.
And so the -- the understood, you know, risk factors, you know, for this are things like alcohol-related liver disease, MASLD and MASH, Hepatitis C. Those things cause chronic inflammation in the liver. Chronic inflammation leads to scar tissue

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formation. And then once a sufficient amount of scar accumulates, that's -- you know, to the point where it's affecting the liver function in some regard, that's -- that's cirrhosis.
HCC does not cause inflammation throughout the liver like a chronic liver disease does, nor does it induce scarring of the, you know, throughout the liver, like a form of chronic liver disease does.
I mean, I'm not aware of any literature that -- that, you know, that kind of identifies HCC, for instance, as a causal factor for cirrhosis. I've never come across that.
The only -- I guess the only scenario where I could see something along the lines of cirrhosis being imputed for someone with a history of HCC is a condition called pseudocirrhosis where someone who has very diffuse HCC in the liver that has been treated many times with different local regional therapies to the point where the liver has taken a lot of damage from the treatments, you can sometimes get a liver that begins to behave as if there is cirrhosis, and that's called

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pseudocirrhosis. But that's -- that's a unique case and -- and not what is typically meant when -- when someone says does liver -- does liver cancer cause cirrhosis.

Q. And so cirrhosis is caused by inflammation in the liver?

A. Yeah. That's -- that's understood to be the pathway. It's things that cause chronic inflammation throughout the liver. That leads to scar tissue accumulation over time, and the amount of scar tissue goes through different stages that are usually defined based on biopsies.

And if there's a sufficient amount of scar tissue and you see certain features on a biopsy that would be diagnostic of cirrhosis if you were to look at biopsies. I mean, these days we don't need to rely on biopsies because we have very well-validated ways of identifying cirrhosis just based on labs, imaging, prediction models, et cetera.

Q. So it's your opinion that HCC does not cause inflammation within the liver?

A. I mean, it's possible that, you know, with HCC there may be some localized

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inflammation potentially around the -- the tumor, but I -- you know, I -- I don't view HCC to be a very strongly inflammatory tumor.

I mean, I know that Dr. Siddiqui made such a comment that HCC is a very aggressive inflammatory tumor. That's -- that's not my conception of HCC, and I don't -- you know, there's no hepatologist that I know of that would say that HCC would lead to cirrhosis in a patient. It's usually the other way around where cirrhosis is the -- the primary risk factor for why someone has HCC.

And HCC certainly does not cause, you know, uniform inflammation throughout the liver like a chronic liver disease would.

Q. Did you do any research for this case on if NDMA caused liver inflammation?

A. Yes, I did. I mean, I came across animal literature, you know, in the course of my literature search that I think was relevant to that question you asked where in the animal literature, you know, where they provide rodents, for instance, with very high doses of NDMA, you know, they would observe things like hepatic fibrosis or scarring in the liver.

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Yes.

Q. Is -- hepatic fibrosis, is that synonymous with cirrhosis, or is there a distinction there?

A. Yeah. Thanks for the question. So I'll clarify that.

Fibrosis is just a medical word that means scar. So fibrosis by itself is not synonymous with cirrhosis. You could have a mild amount of scar, or you can have a very advanced degree of scar.

So when -- if there's very advanced fibrosis, you know, to -- to a certain degree, that -- that then at some point becomes cirrhosis. But the term itself does not -- does not mean cirrhosis.

Q. Can you have advanced fibrosis and still not have cirrhosis?

A. Yes, you can. Advanced fibrosis, the way -- and I admit this is used differently in different literature, but most hepatologists when we use the term "advanced fibrosis," we are referring to two very specific stages of fibrosis.

So just to be very clear about

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that, there -- there -- generally there are four stages of fibrosis in the liver that go from F0 to F4. F0 is totally normal. There's no scar, normal healthy liver. F4 is cirrhosis. There's a lot of scar tissue. F3 is advanced fibrosis but not quite cirrhosis on -- on a biopsy.

So advanced fibrosis usually refers to F3 and F4. So it encompasses cirrhosis, but it also encompasses patients who have F3 fibrosis but not quite cirrhosis yet.

Q. Would -- would some clinicians inarticulately call advanced fibrosis cirrhosis?

MS. ROSE: Object to the form.

THE WITNESS: I mean, I don't know. There -- there may be some clinicians that -- that might use that. I think hepatologists are usually very precise when they use advanced fibrosis or cirrhosis.

I mean, but yes. I -- I can't really speak on, you know, on behalf of other physicians. But it's possible that, you know, some physicians who are not

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attuned to this nuance, they potentially could use that term incorrectly.
BY MR. VAUGHN:
Q. And in your practice, have you ever ran into like a radiologist that might use cirrhosis as opposed to advanced fibrosis?
MS. ROSE: Object to the form.
THE WITNESS: In my experience radiologists, they will use the term cirrhosis. They -- they don't commonly use the term "advanced fibrosis" because the -- the signs that are observed on imaging like a CT scan or an ultrasound, those are -- those have been studied with respect to cirrhosis not advanced fibrosis.
So they're -- they're usually -- yo know, in my experience -- again, I can't speak on behalf of all radiologists out there, but most I'd say well-qualified diagnostic body radiologists they frame things in terms of cirrhosis.
BY MR. VAUGHN:
Q. All right. And then on this web page down here, there's this Penn Liver

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Diseases Program.
Are you part of the Penn Liver Diseases Program?
A. You'd have to click on that to show me what that exactly is.
Q. Okay. And like right here it does say that you are a part of it, right?
Dr. Mahmud, is part of the Penn Liver Diseases Program.
MR. VAUGHN: Can you drop that one in, Kathryn?
And that'll be Exhibit 4.
(Whereupon, Exhibit 4, Penn Medicine Liver Diseases Program, was marked for identification.)
MS. AVILA: Yes. It's in there.
MR. VAUGHN: Thank you.
THE WITNESS: All right. There it is.
Okay. I have it up.
BY MR. VAUGHN:
Q. There you go.
Is that shown on my screen too?
Did that change over to the --
A. Yes. I see it.

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Q. Okay. All right.
And do you see on here it says, "Liver failure can also occur suddenly when the body is exposed to toxins or poisonous substances that severely compromise liver function"?
Do you agree with that?
A. I agree with that in a very specific context.
I can tell you exactly what that means actually. They're --
Q. All right. Go ahead.
A. So -- yeah. So liver failure, what they're referring to here is acute liver failure, which is different than cirrhosis. And the acute toxins that cause liver failure are things like Tylenol, like acetaminophen, or a particular type of mushroom, amanita phalloides, or the -- the death cap mushroom. These are substances that can cause a very acute injury that causes widespread death of liver cells, but it's actually -- it's unrelated to cirrhosis.
It doesn't cause cirrhosis. It's causing widespread death of cells. That

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results in very abrupt failure of the liver that may require transplant.
So that's -- that's, you know, what that, I assume, is referring to as a hepatologist.
Q. Would widespread death of liver cells result in cirrhosis?
A. Generally, no. So the medical term is "hepatic necrosis." So, you know, if somebody developed -- let's say somebody took a bunch of Tylenol, a very, very high dose of Tylenol. That can result in widespread hepatic cirrhosis liver death.
And if you did a biopsy of that patient, you'd see that there's a lot of dead liver cells. But the amazing thing is that your -- a previously healthy liver has a very high ability to regenerate.
And so if the person survives the acute liver failure episode, we would actually expect that patient to regenerate to the point of having the -- more or less the same baseline liver function that they had before taking all the Tylenol.
So no. It's -- it's a distinct

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type of pathologic pathway where it doesn't -- it doesn't typically result in cirrhosis independently, no.

Q. It talks up here about liver problems can be genetically inherited, occurred as a result of disease, or be caused by environmental stressors.

What are environmental stressors?

A. Sorry. Which part did you highlight?

I just wanted to make sure I see the right section.

Q. Well. It doesn't highlight well. Right here.

A. Liver problems -- biostressors.

Yeah. So I think this is, you know, most likely referring to -- you know, so they're listing the common chronic liver diseases, you know, in the section below, you know, Hepatitis B, C, et cetera.

There are many different environmental stressors that different individuals may be subjected to.

You know, NAFLD, which is an outdated term now, but, you know NAFLD or -- or

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MASLD or MASH, nonalcohol-related fatty liver disease, just to put it more colloquially, can be regarded to be environmental stressors.

It's -- it's related to -- to dietary exposures. It's much more common in the United States to see MASLD and MASH than in -- in some other countries because we have very particular dietary exposures.

Alcohol is an environmental stress or in an environmental stressor, and environmental factor that is very relevant to liver disease and cirrhosis in a lot of patients.

So I'd say those are probably the most two predominant relevant ones that contribute to cirrhosis in the United States.

Q. Would carcinogens fall under environmental stressors?

A. I -- I think if there was some carcinogen that was well-demonstrated to -- to cause cirrhosis and cirrhosis comp- -- complications, you could regard that to be a relevant environmental stressor, sure.

Q. Excuse me.

Are there any carcinogens that you

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think do cause liver cancer in humans?

A. Yes.

Q. Okay. Can those --

A. So you know, af- -- you know, for instance, aflatoxin, it's a type of microtoxin that, you know, again, I haven't re- -- reviewed the data in great detail, you know, recently; but that is something that, you know, as hepatologists, we recognized as being something that's associated pretty consistently in different studies with -- with a risk of -- of liver cancer in humans.

Q. Can you think of any other carcinogens that cause liver cancer?

A. So, you know, there's -- I can -- I can list other ones that I've come across literature in the past. The strength of the literature I -- I can't immediately comment on. But other exposures that -- that I've seen, there is some association with -- sorry, androgen exposure.

So particular types of androgen preparations, like testosterone types of preparations in a particular route of administration. There is some limited evidence

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that -- that can be associated with hepatocellular carcinoma in humans.

I think there's also some very limited data about maybe benzene exposure and some aromatic compounds. But honestly, there are not that many major carcinogens that come to mind that have been linked -- you know, I think aflatoxin is the one that comes to mind as being one where there might be a little bit more evidence.

But for each of these, I would have to review the strength of evidence in more detail to make an assessment of -- of how relevant they are in humans. I'll say that all of these things are exceptionally rare exposures.

Q. And does that prevent them from being studies of -- studied as much because it's such rare to be supposed?

MS. ROSE: Object to the form.

THE WITNESS: Not necessarily. I think, you know, many -- many things can be studied using observational studies; and whether or not, you know, a research group chooses to spend time researching

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something is oftentimes based, first, on animal studies. Is there anything potentially relevant to humans to justify doing a study.

You know, my recollection is that there are studies for -- for each of the things I mentioned, but I -- you know, I can't -- I can't speak to the strength of them off the top of my head. I'd have to review them again.

BY MR. VAUGHN:

Q. Do you have an opinion if there's more literature or less literature on benzene causing liver cancer in humans than NDMA?

MS. ROSE: Object to the form.

THE WITNESS: No, I don't have an opinion on that. I -- I haven't reviewed the literature with respect to benzene inasmuch depth as I have with NDMA as pertain- -- pertaining to this case.

But I do recall that there are some studies. I can't speak to the volume or depth of them.

BY MR. VAUGHN:

Q. Okay. And then on this web page we

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were on, it has common liver diseases; and it has cirrhosis as a link.

MR. VAUGHN: If you'd go ahead and drop the cirrhosis one, Kathryn, that will be Exhibit 5.

(Whereupon, Exhibit 5, Penn Medicine Cirrhosis - Symptoms and Causes, was marked for identification.)

MS. AVILA: Okay. It should be in there.

MR. VAUGHN: Okay.

BY MR. VAUGHN:

Q. And for -- the definition of cirrhosis is scarring of the liver and poor liver function.

Do you agree with that definition of cirrhosis?

A. I -- I think it's a very, probably, oversimplified definition of cirrhosis for the purpose of the lay public.

I think I've already given you my definition of cirrhosis, but, you know, I think for -- for simplicity and communicating it to a patient who might be visiting this website, I think it's a -- it's a rudimentary layperson

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summary.

Q. And for -- for the layperson, it would be two things, the scarring of the liver plus the poor liver function to have cirrhosis, correct?

MS. ROSE: Object to the form.

THE WITNESS: Yes. So I mean, I -- I disagree a little bit with the characterization there because, as I've stated before, you can have cirrhosis without having clear evidence of derangement of liver synthetic function. Oftentimes, that is seen later in the progression of cirrhosis.

You know, perhaps -- again, I don't know who makes this website or who's responsible for the content, but, you know, I'm not responsible. I -- I don't -- I don't write this myself. You know, Penn Medicine -- I have no idea who actually writes this.

But I -- I assume it's filtered through a lens to make this very simplistic for patients to just broadly understand what cirrhosis often means.

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And so yes, it means scarring of the liver, and it can mean poor liver function; but as I've stated previously, you can have cirrhosis and actually have relatively reserved liver synthetic markers on your blood work.

BY MR. VAUGHN:

Q. And so do you disagree with the information that Penn Medical is putting out to the public?

MS. ROSE: Object to the form.

THE WITNESS: Like I said, I think that my -- my understanding and nuanced understanding of cirrhosis as a clinician goes much more beyond what, you know, this website is communicating to patients.

I think that, likely, they're trying to keep things very simple to provide at a high level, you know, some understanding of what these medical terms may generally mean.

I don't think their intention is likely to be extremely detailed about the technical definitions of cirrhosis.

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BY MR. VAUGHN:
Q. So do you think it would be more accurate if it had the word "often" before poor liver function: "Cirrhosis is scaring of the liver and 'often' poor liver function"?
Would that be more accurate for you?
MS. ROSE: Object to the form.
THE WITNESS: Again, like I -- I don't have a role in creating this website or curating it to a particular audience.
I think, you know, if -- if I were to -- to generate this myself, hypothetically, I probably would caveat it in some fashion similar to that. It doesn't have to be invariably associated with, you know, poor liver function, but it -- it often is as it progresses.
BY MR. VAUGHN:
Q. Okay. And symptoms, and those symptoms are -- early symptoms are typically fatigue and loss of energy -- energy.
Do you agree with that?
A. I don't uniformly agree with that. That's not -- that is not uniformly seen. That

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can be seen with some particular etiologies of chronic liver disease, but it is very common for someone to have cirrhosis that is compensated and have no symptoms really at all from the patient perspective.
Q. Okay. And so would you also disagree that an early symptom of cirrhosis is weight loss?
A. I wouldn't -- so I guess just to explain, I would not agree that someone that has cirrhosis is guaranteed to have any of those symptoms. They can be associated. Some patients with cirrhosis may have some of these; many may not.
So usually weight loss in the setting of cirrhosis occurs when -- it -- it -- it often occurs in my experience is more advanced cirrhosis. It's not as common of a symptom in early cirrhosis, but there are some patients who do present with progressive weight loss and that are diagnosed with cirrhosis.
So -- so yeah. I mean, I agree that it can be a symptom, but it doesn't mean that you have to have this symptom if you have cirrhosis.

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Q. And Mr. Roberts wasn't experiencing weight loss prior to 2018, correct?
A. I'd have to review his records in detail, but my recollection is no. He was in the range of Class 2 obesity quite consistently for much of his medical record history.
Q. And Mr. Roberts didn't have fatigue or loss of energy prior to 2018, correct?
A. You know, I -- I -- I don't recall that being mentioned specifically in -- in his records. It's -- it's possible that he may have mentioned that as a symptom. You know, it may or may not have been codified by a clinician that was doing their summary.
But that did not come across as being a prominent symptom, you know, during -- during -- well, I think once he had cancer, I think he probably did express some of these things; but early in the medical record, I don't think those were very consistent symptoms that were documented.
Q. Were they ever documented?
A. I'd have to review -- I'd have to review the records again to see if there's specific mentions of fatigue or loss of energy.

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Q. What about small red spiderlike blood vessels on the skin, did you see evidence of that prior to his cancer diagnosis?
A. So that is a specific physical exam finding. There's telangiectasias that you can see oftentimes in the upper chest on patients.
I don't recall off the top of my head seeing that reported in the physical exam, but I also say that it's very common that clinicians will not know to look for it unless they are very cognizant of the risks of cirrhosis. It's -- it's something that a hepatologist would be more likely to look for.
So just because it's not documented by, you know, a -- you know, a primary care physician, for example, in the physical exam, does not mean that that was not there. It could very well have been present.
Q. Are you speculating?
MS. ROSE: Object to the form.
THE WITNESS: I'm not specu- -- I'm not saying that it was or was not there. I'm just providing context to interpreting the medical record that it's possible that things might not be reported in a physical

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exam, but it doesn't guarantee that something was not present --

BY MR. VAUGHN:

Q. Do you --

A. -- for any given patient.

Q. Do you plan to tell the jury that Mr. Roberts might have had fatigue, loss of energy, poor appetite, or weight loss or spider red-like blood vessels of the skin prior to his diagnosis of the cancer?

MS. ROSE: Object to the form.

THE WITNESS: I plan to communicate very clearly that he had very clear evidence of -- of a diagnosis that shouldn't have been made previously of cirrhosis that, you know, predated his cancer diagnosis by -- by quite sometime.

None of that really relies on the symptomatology. I make that assessment based on his imaging and blood work and -- and the prediction scores that I mentioned primarily. It does not rely on his symptoms.

BY MR. VAUGHN:

Q. Okay. Let me go down to exams and

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tests for cirrhosis on Penn's website.

Prior to 2016, did he have a -- or 2018, did Mr. Roberts have an enlarged spleen?

A. Yes. In my view on his -- his April -- let me pull up my report just to -- to give you the right date. I believe it was April 19. Let me just check real quick.

So on my review of his April 19th, 2016, CT scan, my impression is that he had an enlarged spleen; and I believe that was also the impression of the expert radiologists in this case.

Q. What is the normal spleen size for a male -- an adult male?

A. So, you know, I'll -- I'll state that, you know, in general, I -- this is an area of expertise that's more pertinent to a diagnostic radiologist.

In general -- and it might vary a little bit based on which study you might refer to, but somewhere in the ballpark of less than 12ish centimeters is the number that I -- I have in my mind in terms of kind of a -- a certain -- a certain diameter of measurement of the spleen. That's oftentimes regarded to be

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an upper limit.

I've -- I've heard some radiologists say 13 centimeters, but there are also other ways to assess for an enlarged spleen. There are ways of doing volume calculations. Instead of relying on just one axis, some radiologists will do a more detailed assessment where they do measurements in three dimensions on a CT scan to compute a spleen volume. And off the top of my head, I don't recall, you know, what the upper limit of normal is for that.

But when I did my -- my own independent review of the images, I did take the time to do these measurements; and I did reference the upper limits of normal. Again, I don't recall the exact cutpoints for volume off the top of my head; but that was part of my process when I was evaluating that scan for splenomegaly.

Q. What size was Mr. Roberts' spleen when you looked at it in 2016?

A. I don't recall off the top of my head, but I -- you know, I -- I'm happy to re-review it and recalculate this if necessary.

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But, you know, like I said, I -- I had my impression based on my own read, but I'm very differential to a qualified radiologist to make the -- the assessment. And like I said, I believe Dr. Mele and Dr. Chernyak both agree that there is splenomegaly.

And so ultimately, I find their assessment is likely to be the most valid. But, you know, when I was going through the images myself, my own assessment was -- was consistent with what they found.

Q. In your expert report, you didn't list what size you thought his spleen was when you reviewed the imaging, did you?

A. I don't think I listed a specific measurement, no.

Q. Did you take notes anywhere of what size the spleen was when you were looking at it?

A. I don't believe I took any notes. I mean, usually when you make these measurements, you do it directly on the CT scan images. And so I had access to the imaging. I looked through the imaging using an imaging viewer, and there are tools that you can use

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when you're scrolling through a CT scan. There's a ruler function, for example, where you can make measurements.

So I -- yeah. I remember very specifically going through measurements and -- you know, to make my assessment splenomegaly. But yeah. I -- I don't -- I didn't -- I don't think I noted down a specific measurement in my expert report. I just gave the assessment that there was an enlarged spleen.

Q. What program did you use to measure Mr. Roberts' spleen in 2016?

A. You'd have to give me a second to look up the name of the tool. I think it's -- it's called B DICOM viewer.

Q. And does it save the results?

A. I don't know if it does, actually. I suspect it doesn't because every time I've loaded up the B DICOM viewer, I have to reimport all the images. So I don't think it saves specific measurements that I -- I've taken.

Q. All right. And so -- so you're not sure if Mr. Roberts' spleen was just a half of centimeter bigger?

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MS. ROSE: Object to the form.

THE WITNESS: Like I said, I can't give you the exact measurement in this moment. And -- but, you know, I -- I -- you know, if it -- if it's even in question, I would, again, defer to the expert radiologists on both the plaintiffs' and the defense side who report that there is an enlarged spleen.

So yes, I can't give you the exact measurements because I don't recall it off the top of my head.

BY MR. VAUGHN:

Q. And you're aware that his treating physicians at the time did not diagnose him with an enlarged spleen in 2016, correct?

A. Yes, I'm aware of that.

Q. And do you disagree with his treating physicians?

A. Yes, I disagree with that. I disagree with that.

It's -- it's -- it's unfortunately relatively common for -- for there to be variability in radiology reads, and this kind of gets back to prior point about the physical

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exam. Sometimes things may not be a hundred percent accurate in the -- in -- in a particular report. And so you might get some variability from one radiologist looking at it to another.

So that's when you have to look at the -- the qualifications of a specific radiologist. And so if there's a -- if there's a diagnostic radiologist who is very accustomed to reading body CTs with respect to liver disease in particular, there's usually very careful attention paid to the spleen.

So -- and -- and the reason -- you know, one additional reason I think it's important to highlight is the clinical history also matches with an enlarged spleen size. I believe around that time, he already had a low platelet count.

I think I gave you that -- that measurement of thrombocytopenia previously, and I'm happy to explain why it's relevant if -- if you like. I just wanted to find the date of his low platelet count.

Q. Sorry. I'm planning to get to it later if you want to wait. If you want to go

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to it now, you can.

A. Sure. That's okay. We can -- we can save it for later.

Q. Okay. Have you ever diagnosed an enlarged spleen in practice?

A. So I guess you mean -- it depends what you mean by, like, have I ever diagnosed a large spleen.

I -- I definitely communicated a diagnosis of a large spleen to patients. But oftentimes -- you know, many aspects of medicine there are -- there are multiple, you know, physicians that have a role in -- in ascertaining a diagnosis.

So -- so what I would typically do is I would order imaging for a patient, an ultrasound or a CT scan, whatever it might be. I'll look at the images myself, and then I will read the radiology report.

And so if the radiologist reports an enlarged spleen, you know, and it's a radiologist that, you know, that -- that I -- that I'm accustomed to working with that I trust their reads, I will convey that diagnosis to the patient.

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So it's -- it's a loop where I am ordering the study. I'm interpreting the read. I'm, you know, having discussions with radiologists where relevant to -- to communicate what we think is -- is accurate to the patient.

So -- so yeah. It's usually not just based on my own pure assessment. I always refer to the radiology reports to -- to assist with that, given that I'm not a diagnostic radiologist myself.

Q. And so are you relying on the expert opinions either of the plaintiffs or defense in coming to the conclusion that Mr. Roberts had an enlarged spleen in 2016?

MS. ROSE: Object to the form.

THE WITNESS: I would say that their -- their impressions, which I regard to be valid, given that they are diagnostic radiologists with expertise in this area, I had no reason to doubt that.

And my process of looking at images, I -- I like to review the primary images myself just as a -- as a routine so I -- I better understand and contextualize

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what the radiologists are telling me.

For instance, if a radiologist said that there's no enlarged spleen and then I take the time to do a measurement and I look up the upper limit of normal, and it's wildly discordant with the radiologists, I'd have a conversation with them just to make sure that I'm not missing something.

I -- I do this as a secondary check for my own patients just to make sure -- to minimize the probability of errors.

But I think the fact that, you know, two expert diagnostic radiologists on the plaintiff and the defense side agree that there's splenomegaly, I -- I put a lot of weight on that. I'll just say that my own independent interpretation is consistent with that as well, though I give -- I give deference to them and put more weight on their reports given their expertise.

BY MR. VAUGHN:

Q. And you can't tell us what size Mr. Roberts' spleen was in 2016, correct?

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MS. ROSE: Object to the form.

THE WITNESS: Yeah. As I stated previously, I -- I can't give you a specific measurement.

MR. VAUGHN: All right. Now's a good time for a break, Nina.

MS. ROSE: Okay. Great.

THE VIDEOGRAPHER: Off the record at 11:37 a.m.

(Whereupon, a break was taken.)

THE VIDEOGRAPHER: We are back on the record at 11:53.

BY MR. VAUGHN:

Q. All right. Doctor, so I want to stay here on Exhibit 5 where we have on U Penn's website exams and tests for cirrhosis. And we already talked about the spleen.

As far as excessive breast tissue, there was no evidence that Mr. Roberts had excessive breast tissue, correct?

A. Not that I'm aware of.

Q. And prior his cancer diagnosis, there was no evidence he had a swollen abdomen as a result of too much fluid, correct?

A. Yes. I agree with that. There's

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no evidence of that prior to the cancer diagnosis.

Q. And prior to Mr. Roberts' cancer diagnosis, there was no evidence of reddened palms, correct?

A. Not that was documented on exam.

Q. And prior to Mr. Roberts' cancer diagnosis, there was no evidence of red spiderlike blood vessels on the skin, correct?

A. Yeah. I think we already talked about that one in the previous one, but I -- yeah. I did not see any specific documentation of -- of that.

Q. And for small testicles, was there any evidence that Mr. Roberts' testicles had shrunk prior to his cancer diagnosis?

A. And again, I don't recall seeing that in the medical records specifically.

Q. Did you -- did you look for that?

A. Yeah. I mean, I -- I looked through, you know, the document, exam findings.

It's very uncommon for routine office visits to comment on testicular size unless the patient has a particular compliant where they ask the physician to look at the

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testees.
So yeah. I don't recall that ever being the case for him where someone looked at him and documented his testees in their physical exam.
Q. If someone suspected him of having cirrhosis, is that part of the exam that they would do?
MS. ROSE: Object to the form.
THE WITNESS: It is not part of the routine exam, no.
Sorry.
BY MR. VAUGHN:
Q. And so do you disagree with these as far as exams and tests on U Penn's website for cirrhosis?
A. No, I don't disagree with this. I think these are potential exam findings that may be found, but it's --these things are not required to make a diagnosis of cirrhosis.
So I think that's probably why they -- they probably list these things as things your provider may do not that your provider has to do or absolutely will do.
I usually don't, you know, examine

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the testees unless the patient has a particular complaint because it's not a diagnostic criterion for cirrhosis, and many patients find it uncomfortable. So unless there's a specific reason to look for it based on the patient complaint, I won't routinely look at the testees, no.
Q. Okay. And so this part where it says the provider will do a physical exam to look for these things at U Penn, you don't actually do those things, correct?
A. I do most of these things. Like I said, the testees -- the testees might be the exception. I do look for -- just trying to read through this list.
Yeah. I mean, I will assess, you know, spleen size. I will look for evidence of ascites, which is swollen abdomen. I look at the palms in all my patients. I do look at for the -- these telangiectasias, these spiderlike blood vessels in the skin. I look for -- I do look for widened veins in the abdominal wall, and, of course, I look for yellow skin and jaundice.
As I said the only one that I don't

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routinely look for is small testicles.
Q. And Mr. Roberts didn't have any of these prior to 2018 in his medical records, correct?
A. I don't recall seeing any of this documented in his exam, but, you know, I'd have to emphasize these are things that someone with an index of sufficient for cirrhosis would -- would look for. So it's -- it's hard to know if some of these might have been there or not, but they're not documented as such.
Q. And then for tests on liver function patient's complete blood cell count, would that encompass the platelets that you were talking about?
A. Yes.
Q. And then prothrombin time, is that the -- is that similar to the INR time you were discussing?
A. Yes.
Q. Can you explain what those -- is there a difference between those two, or is it the same thing?
MS. ROSE: Object to the form.
THE WITNESS: They're -- they're

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very, very similar. They're -- you know, the INR is sort of derived by the prothrombin time, but I think in -- in general practice, you'll see clinicians mainly refer to the INR. But when you order something like the INR, it's -- it's usually listed as the prothrombin time/INR.
But, you know, in common just discussion among providers, we'll -- we'll typically talk about what the international normalized ratio -- sorry, international normalized ratio.
I'm trying to -- I'll try to slow down for -- for the stenographer. I apologize.
We typically discuss things in terms of the INR, which is used more commonly.
BY MR. VAUGHN:
Q. And when you say prothrombin/INR, is that a PT/INR; is that how it is also abbreviated?
A. Yes. PT/INR is usually -- is referring to prothrombin time/INR.

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Q. Okay. And Mr. Roberts did not have an abnormal PT/INR prior to his cancer diagnosis, correct?
A. I'd have to review them again in detail, but I don't recall him having an abnormal INR off the top of my head.
Q. On the CB- -- I apologize.
On the CBC is there anything you're looking for there besides the platelet count to be abnormal with cirrhosis?
A. Sometimes, yeah. So I think it's -- it's relevant to look at the hemoglobin and the MCV, the mean corpuscular value. The MCV is a -- it's a measure of the size of the red blood cell. I do look at those as well.
And I mean, I look at the white blood cell count. I look at all aspects of the complete blood cell report, but some patients with, you know, more advanced cirrhosis, you may see their hemoglobin or their hematocrit begin to downtrend because they may have bleeding related to their cirrhosis.
So I -- I do look at that as well. That's more in the context typically of patients with more, you know, very advanced

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cirrhosis.
Q. Can you have a normal CBC and still have cirrhosis?
A. Yes.
Q. Can you have advanced cirrhosis and still have a normal CBC?
A. Yes.
MS. ROSE: Object to the form.
BY MR. VAUGHN:
Q. The liver function test that it's talking about here, is that the AST and ALT you were discussing earlier?
A. The liver function tests typically encompasses a number of different labs. It includes the AST, the ALT, the total bilirubin, the theophylline phosphatase, the albumin, and usually the total protein is also reported with that. It's a panel, yeah.
Q. And then the blood albumin levels, you were talking about that as well for advanced cirrhosis, right?
A. Yes. The blood al- -- yeah. It's actually -- it's usually encompassed in the liver function tests that you send. It typically batches those all together. But yes,

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the albumin is another important lab.
Q. And then it mentions some other tests to check for, which includes a CT, MRI, endoscopy, and ultrasound, correct?
A. Yes. I see that there on the page.
Q. Okay. And feel free to look through the exhibit, but they don't mention -- Penn Medical, where you work, they don't mention anything about a FIB-4 study to diagnose cirrhosis, correct?
A. I don't see FIB-4 here. But again, this is a -- like, a public-facing page that I expect patients will go to.
If you try to start talking about prediction modeling and FIB-4 scores, I think that is probably needlessly confusing for the patient. That does not mean that it's -- it is absolutely standard of care best practice for us to use a FIB-4 to help assist with making these diagnoses and understanding the risk of cirrhosis being present or not.
Q. Let's go back to Exhibit 4. There's also a link here to nonfatty alcohol liver disease.
MR. VAUGHN: And if you could drop

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that one next, Kathryn, that would be Exhibit 6.
(Whereupon, Exhibit 6, Penn Medicine Non-Alcoholic Fatty Liver Disease - Symptoms and Causes, was marked for identification.)
MS. AVILA: Okay. It's in there now.
BY MR. VAUGHN:
Q. Doctor, what is nonalcoholic fatty liver disease?
A. So nonalcoholic fatty liver disease, I'll -- I'll first say that this is an out- -- outdated term. So it's -- it's some clear indication that this website -- I don't know how frequently it's updated, but the current term is MASLD, M-A-S-L-D, which is metabolic dysfunction-associated steatotic liver disease.
So I may refer to, you know, the same entity as MASLD or NAFLD, where, you know, depending on convenience or referring to other -- other references from Dr. Siddiqui or elsewhere.
But what I'm referring to NAFLD or

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MASLD is the presence of fat in the liver that is not related to alcohol but is typically related to individuals who have excess body weight who are overweight or obese. It's very commonly associated with other metabolic conditions like high cholesterol, high blood pressure, diabetes. Things like this are oftentimes -- they're very co-associated. They oftentimes present together.

But it's a spectrum of liver disease where when fat is present in the liver in that context, the -- the liver doesn't like that. The fat induces inflammation.

As I explained previously, inflammation over time leads to scar tissue. When more scar tissue accumulates, eventually it can become cirrhosis.

But that's the spectrum generally of what NAFLD and MASLD is.

Q. And do you agree with this part where it says, "NAFLD" -- "For many people, NAFLD causes no symptoms or problems."

Do you agree with that?

A. Yeah. I think I would agree with that. I mean, you know, referring specifically

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to the NAFLD, many people won't even know they have it because, you know, fat in the liver by itself doesn't cause symptoms. I mean, it's possible that, like I said, they might have other co-associated metabolic comorbidities, like high blood pressure or diabetes, that they might have symptoms attributable to those conditions. But specifically related to NAFLD, you know, many patients don't have any symptoms.

Q. Okay. And so fat by itself in the liver does not cause symptoms, correct?

A. For the most part, yes. Yeah. I think that's -- that's fair to say. You know, fat by itself generally does not cause symptoms. There might be exceptional cases where someone has extremely high burden of fat to the point where it's causing a lot of liver enlargement, and that -- that may cause mild, you know, kind of abdominal, vague abdominal discomfort by stretching on the capsule around the liver.

But for the majority of patients with NAFLD, they likely have no symptoms specifically caused by their fat in the liver,

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unless it progresses, you know, to a very advanced cirrhosis.

Q. And then this notes a more severe form of NAFLD is NASH.

What -- what is NASH, and what is the difference between NASH and NAFLD?

A. So here's another instance where I'll introduce maybe two terms because there's also an updated nomenclature for NASH, which is now MASH, M-A-S-H. Which, these entities, again, they refer to the same principle.

But NASH, the acronym is nonalcoholic steatohepatitis. And MASH, with an M, is metabolic dysfunction-associated steatohepatitis. It's all very confusing unfortunately in the world the hepatology.

But essentially, what this is, it means that in addition to there being fat in the liver related to, you know, being overweight, et cetera, there is also inflammation.

Some patients will have NAFLD. They'll have fat in the liver, but it's, quote/unquote, "bland" where there's -- there's fat there, but there's no inflammation.

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NASH and MASH imply that the fat is causing inflammation, and, thus, you know, putting a patient at risk of -- of accumulating scar tissue.

Q. And so would you agree that NAFLD can either have no symptoms or when they do have symptoms, it is fatigue and pain in the upper right abdomen?

A. Yeah. I think I --

MS. ROSE: Object to the form.

THE WITNESS: Sorry.

MS. ROSE: Go ahead. Sorry.

THE WITNESS: Yeah. I think I mentioned that. In some generally uncommon cases, if there's a lot of fat in the liver to the point where all the fat infiltration is causing the liver to become enlarged and stretch on the capsule for the surrounding of the liver, that can give you some of this pain that they're referring to, but it's not -- it's not a very common symptom.

Fatigue is an extremely general symptom, and some patients may have fatigue or not; but -- but oftentimes,

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it's hard to disassociate is it fatigue related to the fat, or is it related to the other metabolic conditions that many of these patients invariably have, like, you know, diabetes, for instance.
BY MR. VAUGHN:
Q. And for the progression of NAFLD to NASH, once you're at NASH symptoms include weakness, loss of appetite, nausea, yellow skin and eyes which is jaundice, itching, fluid buildup and swelling in the legs and abdomen, mental confusion, and GI bleeding, correct?
A. So those are not -- it might be. Those are not specific symptoms to NASH. Many of those are things you expect to see in patients who have NASH that have progressed to cirrhosis.
I think they qualify that there. They say, "In people with NASH who have liver damage (cirrhosis)."
You know, many -- many of these symptoms are related to cirrhosis, and some of them are more specific to even more advanced cirrhosis, not necessarily, you know, NASH itself always.

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Q. And did Mr. Roberts have any of these symptoms prior to his cancer diagnosis in 2018?
A. I don't think he had -- he did not have GI bleeding, mental confusion, itching, jaundice. I -- I can't recall precisely. He may have articulated nausea at some point. So I -- that one I'm not a hundred percent sure of.
But yeah. I don't think he had symptoms of advanced decompensated cirrhosis prior to his cancer diagnosis, just to make that simple.
Q. You say he didn't have symptoms of "advanced decompensated cirrhosis."
Did he have symptoms of just decompensated cirrhosis?
A. Sorry. Let me clarify.
Decompensated cirrhosis, I'm just -- just for lay terminology, I'm referring to that as the more advanced progression of cirrhosis.
The way a hepatologist would discuss this would really just be to think broadly in two different phases of cirrhosis.

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There's compensated and decompensated.
I was just trying to the refer to the fact that decompensated cirrhosis is more advanced progression beyond compensated cirrhosis.
Q. And you agree that cirrhosis is a progressionary disease, right?
A. Yeah. I do agree that -- I mean, the diagnosis of cirrhosis is very much binary, like, we either think it's there or not. But there is a spectrum within cirrhosis where there can been additional progression of scar where things ultimately evolve from compensated to decompensated cirrhosis.
Q. So I want to make sure I'm clear on this.
There's fibrosis. There's advanced fibrosis, and then there's cirrhosis, correct?
A. Yeah.
MS. ROSE: Object to the form. I'm sorry. I didn't mean to interrupt you, Doctor. I want to get my objection in.
THE WITNESS: I will give you more time. I apologize.
So just to be clear, fibrosis,

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again, is just the medical term that means scar. So it's not really specific in terms of any implication of how much scar.
But it's fair to say that there are kind of -- there's minimal fibrosis with very little scar, moderate fibrosis, and then there's advanced fibrosis, which encompasses cirrhosis. These are oftentimes used too encompass cirrhosis, but -- but some patients may have advanced fibrosis but not yet cirrhosis. So they might have F3 scarring, not yet F4 scarring. F4 is cirrhosis. F3 and F4 are used to refer to advanced fibrosis.
BY MR. VAUGHN:
Q. And then once we get to cirrhosis, there's compensated cirrhosis, decompensated cirrhosis, and advanced cirrhosis; is that correct?
MS. ROSE: Object to the form.
THE WITNESS: No. I would just say there's compensated cirrhosis, and then there's decompensated cirrhosis.
BY MR. VAUGHN:
Q. And would you consider

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decompensated cirrhosis advanced cirrhosis?
A. Just to -- I'll -- I'll just be very precise about that.
I mean, so decompensated cirrhosis is defined based on the manifestation of -- of cardinal symptoms of -- of advanced liver disease or advanced cirrhosis. And ascites, confusion related to the liver, which is called hepatic encephalopathy in a particular type of -- of GI bleeding from varicose veins in the GI tract.
If any of those are present, it's referred to as decompensated cirrhosis. That's the medical terminology.
If I say "advanced cirrhosis," I'm doing that just for the benefit of, I suppose, just being able to communicate the principle more easily without having to rely exclusively on the medical terminology, though, if you prefer, I can -- just refer to that as decompensated cirrhosis.
Q. And I --
A. -- but that's what I mean when I --
Q. I appreciate that. That's a helpful clarification.

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So for a layperson or to the jury, using the words like "advanced cirrhosis" could be easier to get that message across than just saying "decompensated cirrhosis," correct?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. I -- I think I -- I can certainly explain decompensated cirrhosis very specifically, but all I'm trying to communicate with the word "advanced" is that there has been progression from a compensated state to a decompensated state.
BY MR. VAUGHN:
Q. All right. Do you see down here on U Penn's website, "A liver biopsy is needed to confirm a diagnosis of NASH, the more severe form of NAFLD"?
Do you agree with that?
A. I do agree with that from a technical -- it's a very technical standpoint, and the reason why I say that is if you're being a medical purist, the only way to state that someone has NASH or MASH is to get a liver biopsy because it's a -- it's technically a pathological diagnosis. You -- it's a -- it's

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a description of the appearance of the liver under a microscope.
So by a very technical definition, NASH or MASH, you can really only technically see it if you're looking at the biopsy.
That being said, these days we do not commonly perform liver biopsy. We do in some scenarios, but far less than we used to. We are able to generally infer if a patient has NASH or MASH without subjecting them to a liver biopsy.
So yeah. I think it's -- it's technically true; but in modern practice, we -- we don't usually routinely put patients with NAFLD and concern for possible NASH through a biopsy. We use evidence from their blood work, for instance, and their fibrosis or their FIB-4 score to infer that there's MASH or NASH occurring that if we did do a biopsy, we would expect to see it.
Q. And Penn Med's website doesn't mention anything about FIB-4 then when diagnosing NASH, does it?
A. It does not. But like I said previously, this appears to be a patient-facing

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website. I don't think this website is comprehensive in describing all aspects of liver disease; but, you know, I can represent to you that, you know, FIB-4 is -- it's, you know, it's codified in, you know, practice guidelines for hepatology and in particular, actually, in surveillance for patients with MASLD or NAFLD, and which terminology you want to use. You know, FIB-4 is used routinely.
Q. And there was no liver biopsy conducted on Mr. Roberts prior to his cancer diagnosis, correct?
A. That is correct. I do recall maybe it was Dr. Ives, I believe, one of his -- his gastroenterologists, at some point early in the records, he had offered him a liver biopsy. I believe he had suspected that -- you know, he had -- he had demonstrated on an ultrasound that there was fat in the liver and in the -- in the setting of abnormal AST and ALT and offered Mr. Roberts liver biopsy. And Mr. Roberts, I think, did not want to pursue that.
Q. And in a liver biopsy, if someone does have NASH as opposed to NAFLD, what --

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what are you looking for?
MS. ROSE: Object to the form.
THE WITNESS: So I apologize.
Can you repeat the question.
BY MR. VAUGHN:
Q. Yeah. Where -- where it says, "A liver biopsy is needed to confirm the diagnosis of NASH, the more severe form of NAFLD," what is going to be in that liver biopsy to indicate that it is NASH as opposed to NAFLD?
A. I see. Right.
So on a liver biopsy, what you expect to see in someone that has MASLD or NAFLD is you expect to see an increase of fat content inside liver cells. That's -- that's what the medical term steatosis means. Steatosis just means fat. You expect to see an abnormal -- abnormal amount of fat in liver cells.
The MASH and NASH part of it means that you additionally expect to see markers of inflammation. You expect to see inflammatory cells, so a certain types of white blood cells. There are also other, you know, particular, you know, kind of pathology-based findings, like

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ballooning, degeneration, and other things that the pathologists may comment on that are also consistent with MASH or NASH.
But broadly speaking, you're looking for evidence of inflammation plus fat not just fat alone.
Q. For the diagnosis of NASH, are you also looking for the presence of cirrhosis or just the presence of inflammation?
A. That's a very good question.
On the biopsy the pathologists will always perform something called a trichrome stage -- trichrome stain, which is a special way of looking at the amount of scar tissue in the liver.
So yeah. It's very routine where in addition to trying to assess what is the chronic liver disease process that is present on a biopsy, they will also report the stage of fibrosis.
So that -- that's where this terminology for F0 to F4 fibrosis comes from. So the pathologists will usually try to make a determination of how much fibrosis or scar tissue is there on a biopsy.

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Q. So am I right in saying that there does not need to be cirrhosis on the biopsy for a diagnosis of NASH?
A. Oh, yes, that's correct. Yeah. Many patients might have NASH, but they don't have cirrhosis.
So you could have somebody that has NASH but only Stage 1 fibrosis. You could have someone that has NASH, but they have Stage 3 fibrosis. Then you can have someone that has NASH, and they have overt cirrhosis F4 cirrhosis.
So you can make -- you can encounter a biopsy across the whole spectrum.
Q. Okay. So the biopsy for the diagnosis of NASH is primarily looking for the addition of inflammation in the liver to distinguish it from NAFLD?
A. Yes.
Q. Okay.
A. Fat plus inflammation is -- is MASH or NASH.
Q. Okay. And we do not have a biopsy showing inflammation of Mr. Roberts' liver prior to 2018, correct?

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A. That's --
MS. ROSE: Object to the form.
THE WITNESS: -- correct.
Sorry.
MS. ROSE: That's okay.
THE WITNESS: That's correct. But as I stated previously, really in this era of practice, we don't routinely perform liver biopsies to demonstrate NASH. We infer it based on a laboratory evaluation, and it's only in scenarios where there's really diagnostic uncertainty where we might discuss biopsy as being an important diagnostic step for a patient.
BY MR. VAUGHN:
Q. All right. And it lists treatments.
And for treatment for NAFLD, it mostly just talks about managing risk factors, correct?
A. So let me scroll through this.
Q. Oh, you're fine. Take your time.
A. Yeah. Yeah.
It does primarily focus on risk-factor management. Although, I will say

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that this page -- I've already stated it looks like it's outdated because they're using the old nomenclature for NAFLD.

But, you know, in the interval -- this is not necessarily so relevant to this case -- but there is now a specific, you know, medical treatment for patients with -- with MASH that's not listed here.

But setting that aside, okay. So it's a relatively recent development. This is otherwise generally accurate. I mean, the main management for MASLD/MASH is lifestyle changes and working on weight loss in particular.

So weight loss is the -- is the primary recommendation. And so things that are in service of trying to promote weight loss are the primary recommendation because the only way to get the fat out of the liver, essentially, is to -- to lose weight, get fat out of the body; and then fat will start to leave the liver, and the inflammatory process will start.

And then, of course, other best practices of management are to not do things that would additionally injure the liver beyond NASH or MASH.

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So that's -- that's where these recommendations of, you know, related to alcohol use and being vaccinated on hepa- -- against Hepatitis A and Hepatitis B, these are measures to further protect the liver from injury.

Q. What treatment options are there now for NAFLD that you mentioned?

A. There's a medication that was FDA approved that's called resmetirom. I'm happy to spell that if you need me to. Resmetirom, R-E-S-M-E-T-I-R-O-M. The brand name is Rezdiffra, and it's a medication that's used for a subset of patients with NASH who have Stage 2 or 3 fibrosis.

Q. Oh, so is it just to treat NASH not NAFLD?

A. Yes, it's used to treat NASH.

Q. Okay.

A. Well, I assume NAFLD encompasses NASH. It's like an umbrella term. But -- but yes, it's specifically indicated with patients that have NASH. You wouldn't use it in someone that had fat in the liver but no inflammation.

Q. And when did that medication come

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to market?

A. It came to market after Mr. Roberts had passed away. I can't recall the exact date. I believe it was in -- you know, off the top of my head, it was probably in 2023.

Q. And prior to that, for NAFLD specifically, the treatment was to manage risk factors?

A. Yes, I'd say so. Yeah.

Q. Okay.

A. Again, minimize -- taking steps to minimize alternative causes of liver disease.

Q. And Mr. Roberts was overweight, correct?

A. Well, he was -- he had Class 2 obesity. So overweight is a specific medical term that refers to a BMI between 25 and 30. And then above 30 is obesity. And then there's different classes of obesity. There's Class 1, which is 30 to 35. There's Class 2, which 35 to 40, and there's Class 3, which is over 40.

So just to be precise, he was fairly consistently in the Class 2 obesity range with a BMI between 35 and 40.

Q. So he was overweight or fat, and

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that then leads to fat in the liver?

MS. ROSE: Object to the form.

THE WITNESS: And again, he had -- he had Class 2 obesity. So it's -- it's -- it's multiple degrees above just being overweight.

But -- but yes. I mean, folks who are, you know, are obese and some who are just overweight can have excess fat in their body, and some of that fat goes into the liver and causes this pathology that we've been talking about.

BY MR. VAUGHN:

Q. And Mr. Roberts weighed about -- what was it about 250 pounds?

A. I don't recall his exact weight in pounds, but I recall his BMI range. BMI is oftentimes a little more relevant because some -- you know, the height of the patient is very, you know, important to know with respect to interpreting the weight.

So his BMI range was very often 37, 38. I think at times it may have been even around 39, but he was very consistently in the range of Class 2 obesity.

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Q. Okay. And he didn't lose weight prior to being diagnosed with cancer, did he?
MS. ROSE: Object to the form.
THE WITNESS: I mean, he -- he's had -- you know, he had minor fluctuations in his body mass index. But it's fairly, you know, consistently documented from a lot of his providers that he's been unable to lose weight despite recommendations to lose weight.
So, you know, he -- he never had really a strong, sustained trend of being able to lose weight it seems like through his own lifestyle changes.
BY MR. VAUGHN:
Q. And did you see in his medical records that he as was attempting most lifestyle changes, such as eating a healthier diet?
A. I don't know to what extent he was, you know, actively operationalizing those recommendations. I know those recommendations were made to him, but, you know, yeah. I don't recall, like, much granular detail that the providers were providing in their notes about

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what specific dietary change he was making or what changes to his exercise routine he was -- he was making.
So I wouldn't be able to give a clear assessment of that based on the records that I recall seeing.
Q. And did you see that he was not drinking alcohol?
MS. ROSE: Object to the form.
THE WITNESS: So from the records, many records say that there's no significant alcohol use; but that was not uniformly the case.
I recall specifically -- so I'm just trying to find it really quickly.
BY MR. VAUGHN:
Q. Uh-huh.
A. Yeah. So October 26th of 2012 --
Q. Uh-huh.
A. -- he was with Dr. Bullard in pulmonology clinic for his obstructive sleep apnea. And in the -- in that documentation Mr. Roberts had been diagnosed with atrial fibrillation, I -- I guess recently prior to that visit. And so I think was providing some

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context around that.
And the quote from the report was he was diagnosed with proximal atrial fibrillation after, quote, "significal [sic] -- significant alcohol intake that occurred at his hunting camp.
So it's not -- it's not totally accurate to say that he never had any documentation of alcohol use. That's one that I recall seeing, and I -- and I documented that in my medical record review.
So at least on that occasion, you know, he reported significant alcohol use to the point where he was diagnosed with an arrythmia.
BY MR. VAUGHN:
Q. And after someone is diagnosed with NAFLD or NASH, they should quit drinking alcohol, correct, or limit alcohol intake?
A. Yeah. I --
MS. ROSE: Object to the form.
THE WITNESS: Sorry.
Yes. I'd say that there's a little bit of a nuance to that. If somebody has MASLD or NAFLD and they have absolutely no

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fibrosis, in my view they don't have to strictly abstain from all alcohol.
The patient's where it's an absolute recommendation are those who have cirrhosis. If you have cirrhosis, it's a strict recommendation from physicians that you should not drink alcohol at all.
Sorry. Excuse me.
But yes. In patients that I'm worried have MASH or NASH and are at a high likelihood of progressing to cirrhosis, I will counsel them to ideally avoid alcohol entirely; and, you know, in the very least, they need to -- to limit their alcohol intake to upper limits of -- of what's generally thought to be safe for males and females.
BY MR. VAUGHN:
Q. And so you found the record in 2012 of him drinking on a hunting trip.
Do you have any evidence of him drinking after that time point?
A. No. I don't -- I don't recall seeing any consistent documentation after that where, you know, where -- where clinicians were

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thinking that he was drinking a significant amount or nothing that was really reported by him, as best as I can tell.

Q. And did you see in the records of him being physically active, such as going on hunting trips throughout 2012 through his diagnosis of cancer?

A. I recall that instance of the hunting trip, and there might have been a fishing trip mentioned somewhere else. I may be misremembering that, but I don't know. You can -- it's kind of debatable how active a fishing trip or hunting trip are. And, you know, I don't know what regularity Mr. Roberts may have engaged in -- in these types of activities.

So it's -- it's tough from the record, in my view, to get a really strong sense of how much physical activity he was engaged with in the course of his kind of routine care during the course of his medical record history.

Q. And he was taking medications to manage his blood pressure and diabetes, correct?

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A. Yes.

Q. And he did not have Hep A or Hep B, correct?

A. Correct.

Q. Do you know if he was vaccinated against such diseases?

A. Sorry. Let me look at my report.

Yes, I do. I just wanted to pull it up because I wrote these labs down. I just wanted to make sure I present it to you accurately.

So on July 18th of 2018, a lot of that relevant laboratory data had been sent off, I believe, by Dr. Hooks his -- his gastroenterologist.

And so he had some Hepatitis A and B related serology data. So his Hepatitis A antibody was nonreactive. They don't report if that's an IgG or IgM antibody, which would be relevant. But most of the time when a lab reports it that way, it's the IgG antibody that is nonreactive, which would imply that he was not vaccinated against Hepatitis A.

However, Hepatitis B he had surface antigen nonreactive, Hepatitis B core antibody

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non reactive; but the Hepatitis B surface antibody was detected at a level of greater than 11.5.

So my interpretation of that is he was never infected or exposed to Hepatitis B virus, which is why the surface antigen and the core antibody were negative; but he had immunity. He was -- he was likely vaccinated against Hepatitis B because he had the antibody detected.

Q. And was he on medication to lower his cholesterol and triglyceride levels?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I -- again, I don't believe for much of his history. I don't recall him being treated with a statin, which is what's typically used for controlling, you know, high LDL levels.

But he did carry a diagnosis of hyperlipidemia that was reported in November of 2006, but I don't recall him really being on a lipid-lowering agent certainly later in his medical record history. I don't recall that being really clearly demonstrated even in his early

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medical history.

BY MR. VAUGHN:

Q. Did he have elevated cholesterol and trigly- -- triglycerides?

A. Yes. He definitely had an elevated LDL and triglycerides. I wrote down some of those. So for instance, September 20th, 2005, he had a triglyceride value of 390, a cholesterol value of 230.

And on November 14th, 2006, he had an LDL that was very clearly elevated at 153.

So that's usually -- LDL is what is most commonly used, you know, from my understanding, from primary physicians and cardiologists to make decisions primarily about the need for medications like statins to lower LDL, which is oftentimes referred to be the, quote/unquote, "bad cholesterol."

So an LDL of 153 is -- is elevated.

Q. Is Crestor a statin?

A. Crestor is a statin. Yeah.

Was he on Crestor?

I -- I just can't recall if he was or not. He might have been on -- if he was on Crestor, then that is a statin at that time

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point. I just don't recall seeing that reliably later in his record.

Q. So as far as managing his risk factors for NAFLD, he was basically doing everything except for actually losing the weight, correct?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I think in terms of managing the comorbid conditions associated with MASLD and NAFLD, which are things like hyperlipidemia, hypertension, diabetes, if you're representing to me that he was on Crestor and that it is just slipping my memory, then I'll take you at your word that he may have been on Crestor. That would be appropriate management for -- for hyperlipidemia.

I know he was on medications for hypertension, of course, different ones over time. I think around the time of his hyperlipidemia, he was on Celiprolol and hydrochlorothiazide. And later was -- was switched to different agents.

And then later in his history with diabetes, he was on Metformin and another

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medication, a secondary medication for diabetes.

So yes, I would agree that generally speaking, he was receiving pharmacologic therapy for those comorbid conditions. However, as I said previously, the most important central aspect of managing MASLD and NAFLD and the only thing that's effective is weight loss and demon- -- demonstrability to achieve sustained longitudinal weight loss. And without that, the NAFLD and the NASH -- the MASLD and the MASH, they won't go away; and they'll continue to cause liver injury and eventually cirrhosis.

So the comorbid conditions that -- that come along with this is a package oftentimes because weight is the underlying thing that is the central risk factor for all those conditions is the root cause. And I don't think the root cause of all of those things was being managed. I mean, he didn't lose weight, unfortunately.

You can almost think of the

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medications as being a Band-Aid on top of the root cause to try to mitigate the injury related diabetes, high blood pressure, high cholesterol. But the root cause is the weight, and that was not addressed successfully really at any point in -- in his history.

BY MR. VAUGHN:

Q. Do you think Mr. Roberts got liver cancer because he was overweight?

A. I think that -- again, he was Class 2 obesity, not just overweight.

I do think that obesity was part of the picture. I don't think it's the entire explanation. I think it's related to why he developed cirrhosis, and I think it also has some independent contribution to the increased risk of liver cancer.

So it's -- it's not an isolated thing. I don't think it's just the Class 2 obesity. It's really the process -- the main thing in my view is the process of MASLD and MASH progressing to cirrhosis. Because once there's cirrhosis that -- that is, you know, the best established risk factor for developing

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hepatocellular carcinoma.

So insofar as, you know, it's related to causing cirrhosis and has some elevated independent risk beyond that, so it's part of the picture; but it's not the entire explanation.

Q. If Mr. Roberts was not obese, do you believe that he would have developed cancer when he did?

MS. ROSE: Object to the form.

THE WITNESS: So I mean, you're giving me a hypothetical. So -- so, you know, I'll answer that, you know, with that in mind; and I'll -- would you like me to assume that everything else is in the same?

So he --

BY MR. VAUGHN:

Q. Correct.

A. -- is not obese?

Okay. So if you take out. It's a little bit tough to tease out entirely because the obesity is interrelated to things.

If he wasn't obese, if he was a completely normal weight, he would be less

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likely to have MASLD. He'd be less likely to have NASH. He'd be less likely to have diabetes, high blood pressure, hyperlipidemia, coronary artery disease.

So in that hypothetical, he would be a much, much healthier patient. So it's -- it's hard to perfectly project what would have happened. But if he was a normal weight, there's a very good chance that he would have never developed cirrhosis; and therefore, you know, there's a very good chance that he would have never developed hepatocellular carcinoma. Yes.

Q. And -- and so to be clear, it's because he was overweight, he developed cirrhosis, in your opinion; and then the cirrhosis led to his cancer?

MS. ROSE: Object to the form.

THE WITNESS: That's not what I'm saying.

I said that there are multiple important risk factors to consider in this case. Cirrhosis is one of them. And there are multiple factors that are related to his developing cirrhosis,

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including Class 2 obesity as well as MASLD and MASH and -- and diabetes for -- for that factor.

But, you know, as I state in my expert report, it's not just the cirrhosis. You know, diabetes, obesity, MASLD, and MASH, those are also independent risk factors for hepatocellular carcinoma.

And just to make that really crystal clear, a very good demonstration of that is the fact that many patients with MASH develop hepatocellular carcinoma in the absence of cirrhosis.

So cirrhosis is not a prerequisite state. It's -- it is a very, very high risk state for liver cancer, but the other factors matter too, independently.

BY MR. VAUGHN:

Q. On the outlook or prognosis for NAFLD on Penn Med's website it says, "Many people with NAFLD have no health problems and do not go on to develop NASH."

Do you agree with that statement?

A. Not really, honestly. It's a -- I

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think it's maybe -- I'm not sure if they're referring specifically to NAFLD-related health problems, in which case maybe it's a fair statement.

My position generally is, as I've stated, many patients with NAFLD, they tend to be overweight. They tend to be obese, and that puts them at a higher risk of having other problems like diabetes, high blood pressure, high cholesterol. It's a very, very well-demonstrated association, you know, including features of the metabolic syndrome. These are co-associated.

So perhaps what they're referring to there is just NAFLD-related health problems, which I think is fair. But I think my -- my -- my perspective is I probably would have written that a bit of a different way because patients with NAFLD are more likely to have these other important comorbidities.

Q. Do you agree that many people with NAFLD do not go on to develop NASH?

A. Yeah. I would agree with that. Many patients, you know, have bland fat in the liver and -- and don't develop NASH. There's a

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subset of patients that do.

Q. Can you give me an approximate percent of people with NAFLD that go on to develop NASH?

A. Yeah. I don't want to give you the wrong figure. I mean, I can give you ballpark estimates of some of these things. But, you know, yeah. I'd have to really kind of look at the literature again to give you really precise estimates.

But roughly a third of individuals in the United States have NAFLD. We are, unfortunately, a very generally obese country with poor lifestyle habits. So NAFLD is very, very common. One in three people have it.

You know, NASH develops as a subset. I don't know exactly know, you know, what proportion may have NASH. But -- but broadly speaking, there's roughly -- there -- I think of it in terms of kind of -- if I see a patient with NAFLD, I can give you estimates for timeframes of progression to other phases of -- of -- of fibrosis that informs sort of the risks of NASH and then cirrhosis.

If you see a patient with -- with

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MASLD or NAFLD, they typically will -- you know, there's a risk of progressing to the next stage of fibrosis in about five to seven years.

So through that lens, you can sort of get estimates, you know, broadly of how many patients will progress these stages to have significant MASH and then cirrhosis, but I don't have a really precise number of, like, what proportion of patients with NAFLD have NASH. I don't know if we necessarily have really accurate estimates of that honestly.

Q. Would you agree that most people who are obese have NAFLD?

A. That's probably the case that most people who are obese likely have NAFLD or MASLD, yes. I don't know exact -- the exact proportions, but I would expect that most individuals do have fat in the liver if they're obese.

Q. Okay. We were talking about how losing weight can help treat or reverse NAFLD.

Does that mean that the fatty deposits within the liver can be reversed?

A. That's a very good question, Counselor.

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I'd -- I'd say that, yes, there's very good evidence that a sufficient amount of weight loss can lead to resolution of fat in the liver.

So fat will leave the liver, usually it's -- it's in the ballpark of 7 to 10 percent of body weight that needs to be lost to achieve fat coming out of the liver and, therefore, resolution of steatohepatitis or MASH or NASH.

But it's important to state that even if fat is -- is gone after significant weight loss, the scar -- any damage that's resulted from the process is still there. The scar does not -- does not reliably go away.

Q. And that was going to be my next question.

Is scarring or fibrosis of the liver reversible?

A. So it's actually a very interesting area of -- of -- of research because generally, you know, the canonical thinking was that fibrosis generally was not reversible. And -- and for the most part, I think that's still accurate, but I think, you know, we're finding

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that some patients might get a little bit of improvement if -- when they're appropriately managed. You can some reduction in the degree of scar, but typically not total resolution.

To give you just an example of where that literature -- excuse me -- comes from or maybe just explain this in a very lay -- lay -- lay terminology really quickly.

Scar in the body is very similar to scar that you can see on the outside. So like, if you're a kid and you fall and you cut your knee and you get a scar there, you usually have that scar there your whole life. It's generally the same principle on the inside. So if you have something that causes scar inside an organ, that tends to also stick around your whole life.

But -- but we know from some studies -- and this is primarily from the bariatric surgery literature -- where some patients that have NASH or MASH and they've undergone a biopsy in these studies to demonstrate how much scar they've had.

So some patients in these studies, they'll have Stage 3 fibrosis on the biopsy.

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They then undergo a bariatric surgery like a Roux-en-Y gastric bypass, which is very effective in causing significant weight loss. Like, a Roux-en-Y gastric bypass patient might lose 30 percent of their body weight over the course of a year. So they -- they definitely achieve that benchmark of 10-percent weight loss.

If you take a patient like that and then do a biopsy a year or two after they've lost all that weight, sometimes their fibrosis stage has gone from a three to two.

So we know that there's some potential to improve fibrosis if the patient achieves a lot of weight loss. But -- but it's -- it would be very unusual to go from Stage 3 to completely normal. That -- that generally is not seen.

Q. And then the same type of question for cirrhosis.

Is cirrhosis reversible to any degree?

A. You're asking very -- really good questions. These are questions that patients ask all the time too.

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Historically, we do -- we -- we don't -- usually once we make a diagnosis of cirrhosis, we regard the patient to have cirrhosis moving forward, and we manage them with the assumption that there is cirrhosis.

There are some scenarios like very specific scenarios, where patients may have some improvement in their -- their estimated fibrosis, very, very specific scenarios. And one scenario is Hepatitis C virus. That's probably the best studied one where a patient has chronic Hepatitis C. They develop cirrhosis, and then they're treated with a medication that can cure the Hepatitis C entirely.

Those medications were, you know, developed in, like 2015, 2016. And so now we're able to cure Hepatitis C, and we've observed over the past decade or so in following these patients, that some of those patients might go from F4, which is cirrhosis, to F3.

The reason why I say it's a pretty exceptional circumstance is a lot of those patients the only reason -- the only cause of

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their liver disease was Hepatitis C, and there's a very abrupt -- abrupt and complete removal of that underlying cause of liver disease. So that doesn't really translate to -- to MASLD and MASH for the vast majority of patients where, you know, to achieve that abrupt transition, you need to have substantial and sustained weight loss, which unfortunately, is very tough for patients to the achieve.

MR. VAUGHN: Nina, I'm at a great spot for a break if you want to do lunch now.

MS. ROSE: Yeah.

Does that work for you, Doctor?

THE WITNESS: Yeah.

THE VIDEOGRAPHER: Off the record, 12:45.

(Whereupon, a lunch was taken.)

THE VIDEOGRAPHER: We are back on the record at 1:25 p.m.

BY MR. VAUGHN:

Q. Welcome back, Doctor.

A. How are you doing?

Q. Good. Earlier we were talking about how platelet counts are part of the CBC,

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correct?

A. Yes.

Q. And would thrombocytopenia be an abnormal CBC result?

A. Yes, generally. Yeah. If the platelet count's less than 150, that would be regarded to be an abnormal CBC.

Q. I want to go back to your expert report, which was Exhibit 1. I'll go ahead and screenshare it, but feel free to look at it yourself as well.

A. Okay.

Q. I want to go to page 18 right now. I, first, want to direct you to this part of your opinion, which is, "Cirrhosis refers to significant scar tissue that impairs liver function."

You agree with that, correct?

A. Yes.

Q. Okay. And that -- and that is what Penn Medical is saying as well, correct, that it's both the scar tissue plus the impaired liver function?

A. Yes.

Q. Okay. And then you start talking

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about FIB-4.

Is that what you were discussing earlier as far as being able to diagnose cirrhosis with?

MS. ROSE: Objection to the form.

THE WITNESS: Yeah. Not -- not -- not in and of itself to diagnose the cirrhosis, but as a tool to risk stratify -- risk stratify patients with chronic liver disease who may require further testing to -- to rule in or rule out cirrhosis.

BY MR. VAUGHN:

Q. And within Mr. Roberts' medical records, does it ever mention FIB-4?

A. I did not see any mentions of FIB-4.

Q. And you note that a FIB-4 of less than 1.3 effectively rules out advanced fibrosis.

Can you explain that?

A. Sure. So if you calculate the FIB-4 for a patient, again, based on the age, AST, ALT, and platelet count, if you get a very low number, less than 1.3, that -- that patient

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is extremely unlikely to have advanced fibrosis.

And as I stated previously, advanced fibrosis, that -- I'm referring to F3 or F4 fibrosis, which I think I say a little bit higher up in the paragraph.

Q. Understood. And then you note, "A FIB-4 greater than 2.67 has an 80-percent positive predictive value of having cirrhosis."

Can you explain that?

A. Sure. So if you calculate the FIB-4 in the same way that I just mentioned, if the value is over 2.67, what I mean by 80-positive predicted value of having cirrhosis, if you had 100 patients and all 100 had a FIB-4 over 2.67, around 80 of them would, in fact, have cirrhosis.

Q. And you noted, "A FIB-4 above 2.67 denotes a very high risk of advanced fibrosis."

What is that based on?

A. Right. So that's -- sorry. I'm trying to see exactly where that is on -- on my screen as well.

Yeah. Right. So I'm drawing a contrast there between the low FIB-4 value in

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the previous sentence where I'm just trying to put into context what a low FIB-4 means in terms of negative predicted value and then drawing back to the statement I just made that if you have a high FIB-4 that, you know, a high proportion of those patients will have cirrhosis or advanced fibrosis.

Q. And what's your basis for saying that above a 2.67 is very high risk of advanced fibrosis?

A. Yeah. So that's -- this has been studied quite extensively in the context of different liver diseases, so including, you know, things like MASH and MASLD.

I, you know, that -- that -- you can look at the National Hepatology Society guidelines that comment on this as well as specific studies where they look at patients, you know, with MASH, MASLD. They cap at the FIB-4s, and they basically correlate that with biopsy findings to see what cutpoints, you know, reliably differentiate patients with really minimal scar versus advanced -- advanced scarring. And that's how they arrived at those -- those types of calculations like

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positive predictive values.

Q. And then you note that FIB-4 between 1.3 and 2.67 are an intermediate range for advanced fibrosis and cirrhosis.

What is your basis for those numbers?

A. Yeah. That -- that comes from guidelines as well as the literature that I was referring to in my previous response.

So basically, the FIB-4, we think of there as being kind of three potential buckets. Either it's very low, in which case you've effectively ruled out advanced fibrosis. It can be very high, in which case the patient has a high risk of having advanced fibrosis or cirrhosis. Or it can be in this indeterminant range in between, which is sort of the gray zone where the patient, you know, they -- they may have cirrhosis. They may have advanced fibrosis, but they need, you know, some additional dedicated testing to clarify how much scar tissue they may have.

Q. Is intermediate risk the same as moderate risk?

A. I'm not saying intermediate. It

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says indeterminate. So it can't be -- it can't concretely stated based on the FIB-4, you know, if they do or do not. They need further evaluation, further testing.

Q. Thanks for clarifying that. I was reading cross-eyed apparently.

A. That's okay.

Q. When did FIB-4 start being used in practice; do you know?

A. I can't give you a really precise, you know, month and year exactly, but it's become much more commonplace in the past several years of practice. I would not have expected to see it, you know, throughout much of Mr. Roberts' medical record.

It certainly was not widely used or studied, you know, in 2006, 2007, even, you know, 2010, '15, et cetera. So I'm not surprised that FIB-4 was not computed. It's really in the past couple of years where there's really been much more of a widespread education for primary care physicians to know to screen this, to screen, you know, their patients using FIB-4s to identify patients who may have cirrhosis and need to be referred to a

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hepatologist.
In the past few years, it's been codified in, you know, in different guidelines. You know, for example, the American College of Gastroenterology -- sorry, American College of Gastroenterology guidelines, you know, includes FIB-4 in the diagnostic algorithm to identify patients who may have cirrhosis or need further evaluation.
So -- so I can't give you precise date; but the past few years, it's become much more well-recognized and communicated in guidelines.
Q. And so this is a new methodology?
A. It's relatively new. I -- I think -- I -- I don't know when this 4 was first published. I can't recall off the top of my head, you know, when the first -- or deriving this was published.
But initially, it was more specifically to the Hepatitis C literature. And the way -- the reason why I say it's more in the past couple of years is because it was subsequently studied in detail in MASLD and MASH patients.

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And given that, you know, MASLD and MASH is a -- is one of the predominant causes of liver disease in the United States now, it's -- it's been a priority to educate, you know, primary care physicians about using the FIB-4. And somehow systems have gone so far as to integrate it into the medical records system to automatically calculate it and present it to a primary care to -- to prompt them to -- to take action and triage the patients appropriately.
Q. Are there still some facilities that don't do FIB-4?
A. I mean, I'm sure there is -- you know, as with any guideline, there's practice variation, you know, some practitioners that might not be following the literature or best practice state-of-the-art guidance.
I have no doubt that there are practitioners out there that don't know about the FIB-4 or don't use the FIB-4; but, you know, nonetheless, it is the state-of-the-art for medical practice. It's codified in our guidelines.
Q. When did you first learn about

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FIB-4 scoring?
A. I was -- I can't recall the specific year, but, you know, I -- I've certainly been aware of it, you know, as long as I've been a hepatologist.
But like I said, it was more originally in the context of more Hepatitis C; and then subsequently when it was studied in the setting of MASLD and MASH -- I mean, it's certainly has been much more prominent I would say in the past two to three years where it's been a central point of -- of our -- our risk management and algorithmic denitrification of cirrhosis at the population level.
Q. When did you start computing FIB-4 scores as part of your practice?
A. I see. I've been routinely for at least a couple of years.
Q. What patient population do you use the FIB-4 score with?
A. I use it broadly, but some of the cutpoints differ a little bit depending on the etiology of liver disease. You know, most of my patients these days -- in the Veterans Hospital is where I take care of a lot of

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patients.
Most of the patients have Hepatitis C alcohol or FIB-4 -- I'm sorry, or MASLD/MASH. Probably the majority have -- have MASLD and MASH.
So those are the -- the settings where I primarily use it, but I'd say predominantly Hepatitis C and MASH.
Q. Do you know how the FIB-4 score was developed?
A. So I can provide you with my recollection. I mean, I would have to find the seminal studies to look at the methodology in detail, but I can -- I'm happy to provide you with my general recollection of -- of the type of approach.
Q. Great.
A. Yeah. So similar to what I said, the researchers that develop this score and similar scores -- there are other scores similar to this that have been developed. Actually -- actually, I can probably be more concrete because I know the person that developed this. It's Richard Sterling. He's a hepatologist currently at BCU. Sorry. It's

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coming to -- more recollection is coming to me as think about this because I'm remembering conversations that I've had with him.

It probably was developed some time ago, but it might even have been, you know, a decade, honestly, when it was first developed. But regardless, Dr. Sterling, if I'm recalling this correctly, he -- he thought about, you know, labs that were plausibly related to cirrhosis first. AST, ALT, platelet count for some reasons have articulated -- some that I have yet to explain are important when you're re-stratifying patients for cirrhosis.

I think I've explained the relevance of platelet count, how that starts to go down when someone develops cirrhosis and elevated pressures in the portal system behind the liver. So platelets are very important.

AST and ALT in the setting of cirrhosis something interesting and unusual happens -- not unusual, but something interesting happens, where they -- the levels can actually start to go down over time. And the AST in particular will start to rise relative to the ALT. So the ratio becomes,

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oftentimes, a little bit more skewed towards AST being a little bit higher than the ALT.

And so the score -- the formula that's used for this has a ratio of AST and ALT, and then it has platelets as a factor. I think it's multiplied by that. The square root is in the formula somewhere, and then age factors in.

But that was the plausibility for why those factors were important and they were hypothesized to be this way.

So Dr. Sterling and colleagues, you know, they -- they -- they started from that point about what factors were plausibly related and important, and then they, I think, fit a variety of formulas from different types of models, I -- I expect and correlated that against biopsy results in patients.

And then they identified -- okay. Let's say they had a patients. I'm not sure how many they had in their initial study. But hypothetically, if they had a patients from diverse degrees of scarring, some patients might have F4; some have F1; some have F2, et cetera. And they look at different

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cutpoints for those patients for FIB-4, and they identify what threshold beyond which are we really well-separating patients that have cirrhosis and what's the opposite case? What -- what low threshold are we really adequately separating patients who clearly don't have cirrhosis.

That's the general methodology that -- that I, you know, I think was used in this case. But, you know, I haven't -- you know, I haven't reviewed that particular study in a long time, and I really can't recall exactly what year it was. But the more I think about it, it must have been -- gosh, it might even have been a decade ago, if not more. I'm not sure.

Because I -- I had this conversation with Dr. Sterling. Sorry. Too much of an aside, but when I was interviewing for hepatology positions -- and that was in 2019, 2020, and so at that time I met with him; and we discussed the FIB.

So it was clearly in prac- -- it was clearly present at that time and likely for sometime prior.

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Q. And does it matter how many patients it was initially studied in to be developed to?

You he said it might have been a hundred?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I mean, sample sizes matter to provide estimates of -- of accuracy, diagnostic and predictive accuracy of any store; but oftentimes, it's more important are subsequent validation studies, where other researchers will take the tool or the formula and apply it in their own cohort of patients or in patients who have different types of liver disease.

I alluded to that before that, you know, Hepatitis C was one of the earliest use cases and most important use cases for FIB-4. But subsequently, there have been a variety of studies where FIB-4 has been studied specifically in patients with MASLD and MASH to identify the cutpoints that I -- that I stated in my expert report.

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So -- so yeah. It's not -- I'm not basing this on one study. There are a variety of different validation studies across different patient contexts and different patient cohorts that inform the diagnostic accuracy of these tools.

BY MR. VAUGHN:

Q. At the time you met with Dr. Sterling, was FIB-4 being used in that MASLD patients, NAFLD patients?

A. I honestly can't recall if it was being used in MASLD and MASH patients at that time.

Q. Was there a time it wasn't being used in those patients?

A. I expect that -- you know, most doctors, you know, practitioners they wait for the studies of external validity or specific validity in different populations. So I -- I expect that, you know, when it first came out -- and part of my recollection here is challenging because I wasn't a hepatologist at the time it was being used primarily. So it wasn't part of my practice obviously when I -- you know, prior to my hepatology practice.

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But I expect there probably was a time where it was really primarily being used in Hepatitis C. It was only after, you know, these validation studies in MASLD and MASH patients came out that there was increased confidence and demonstration of cutpoints that can be reliably used in those patients.

Q. And so are you not aware what patient population the FIB-4 index was initially developed with?

MS. ROSE: Object to the form.

THE WITNESS: As I said, you know, I -- I don't recall exactly. My -- my recollection -- my loose recollection is, you know, I believe it was primarily in Hepatitis C patients, though, I'd have to look back at literature and -- and check.

What I can say now in the current state of practice, it is standard to apply this across multiple etiologies liver disease and definitely in patients with MASLD and MASH.

BY MR. VAUGHN:

Q. What are the limitations of the FIB-4 index?

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A. That is a good question. Some of the limitations of the FIB-4 index are you do need to interpret it in -- in the context of what's happening with the patient. For instance -- and this is actually relevant in patients with alcohol-related liver disease.

If they -- if a patient with alcohol-related liver disease is very heavily drinking, that can cause the AST to rise more than the ALT; and that can impact the validity of the FIB-4 performance.

So it's -- it's best -- it's really best applied in scenarios where there's a stable baseline, you know, labs for patients. That obviously is less relevant for MASLD patients because by definition, they don't have significant alcohol exposure. That's one context.

The other context is sometimes the platelet count can be invalidated in some patients where it no longer becomes a good proxy for portal hypertension and -- and liver disease and cirrhosis.

The main context for that are things like if someone had their spleen

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removed, the platelet count rises substantially. And so they'll have a very elevated platelet count. And so it's no longer reliable to use the FIB-4 in that type of patient.

Or a patient that has some specific autoimmune types of conditions that could impact the platelet count. One instance is something called ITP, idiopathic -- idiopathic thrombocytopenia.

So you have to understand, like, the particular patient context to understand if the AST, ALT, and platelets are reliable for the purpose you're trying to apply them. That -- those are the major limitations. And, of course, you know, interpreting the diagnostic accuracy. Like I said, it's not a hundred percent accurate for ruling in cirrhosis, which is why further testing and corroboration is needed.

But, you know, 80-percent positive predictive value for a screening test is quite good.

Q. And so like you were saying, the platelet count makes a big determination in the

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final value of the FIB-4 score, correct?
A. Yes. I'd say so.
Q. And so it's very important to investigate any causes that might drop or increase someone's platelet count, correct?
A. Yes. I'd agree with that.
Q. And you mentioned Dr. Sterling is the one who developed the FIB-4 index.
Would you defer to him on the specific weaknesses and strengths of the FIB-4 index?
A. No, I wouldn't defer to him. I think that this is so widely used in hepatology practice now that, you know, I -- I was able to kind of articulate to you very clearly, like, multiple specific examples of limitations; and that's informed directly by my clinical experience using the FIB-4.
So I think that because so many practitioners have experience using this in practice, we understand the boundaries of, you know, when it's appropriate to apply, when you need to be cautious, and things like that.
Q. Do you believe that -- crashed that. Sorry.

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So you believe you have more expertise in the FIB-4 index than Dr. Sterling?
MS. ROSE: Object to the form.
THE WITNESS: Well, I'm not sure in what respect you mean that question. Maybe you can clarify, like, what -- what specific element of the expertise?
Like, Dr. Sterling certainly is more knowledgeable about the specific design and cohorts that they -- that was used to derive the score than I would be.
But I would say that I'm, you know, I'm very comfortable using it in practice and have used it and -- and, you know, am aware of some of these validation studies that have been performed in the context of MASLD and MASH, which is what's relevant to this specific case.
BY MR. VAUGHN:
Q. Is age part of the calculation when doing a FIB-4 score?
A. Yes.
Q. Is there any limitations by using age in a FIB-4 score?
A. I would say so, yes. At the

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extremes of age, patients become a little bit more likely to have higher scores. And generally, that's appropriate in -- in most instances because, you know, the longer you've been alive, the more likely it is you 'e accumulated more scar. And that's part of the reason why age is in there is my understanding.
But there can be scenarios where if a patient has not really been demonstrated to have longstanding, preexisting chronic liver disease and age is the driving factor for a FIB-4 being elevated. My suspicion is that it's a little bit less accurate in that setting.
Q. And in this case for Mr. Roberts, how did -- scratch that. Sorry. I'm going to get a drink.
MS. ROSE: Your sickness has finally caught up to you.
MR. VAUGHN: No kidding.
BY MR. VAUGHN:
Q. In this case for Mr. Roberts, how did you calculate the FIB-4 score?
A. So I took his age at a particular -- at the time the lab was drawn. I

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took an AST and the ALT and the platelet score, and then I put it into -- yeah. We have tools that we use in practice to -- that have these formulas in apps on or websites, for instance, to facilitate calculation or computation of the FIB-4.
So the app that I most commonly use is something called MDCalc, M-D dash C-A-L-C [sic], very commonly used by lots of folks, not just in hepatology, but across the field of medicine. It's a repository for lots of prediction scores.
And so if you go to MDCalc, you can look up the FIB-4 score. You can input the age, the AST, the ALT, the platelet count, you know, click on the calculator or computer, whatever the button is; and it gives you the -- the score.
So that's -- that's my general process. I looked at his data from particular dates when he had his lab reports reported. I looked at his age at that time, and I computed his FIB-4.
Q. And did you use the app to do the calculation, or did you use the website?

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A. I don't recall. I believe they're the same one. It obviously looks different on -- so I don't have the -- let me see. I think I can tell you if I have the app on my phone or not. That might help me answer the question. That's okay.

I do have the app on my phone. There is an app on the phone. I don't honestly remember if I navigated to the website or if I used the app. If I had to guess, I probably used the app because I used the app when I see patients.

So most likely I used the app, but my understanding is the formula and the computations would be the same if you used the app versus going to the MDCalc website.

Q. All right. And you wrote your expert report just about a month ago, right?

A. I believe so, yes. Yeah.

Q. And the website you're referencing that has it, is that Dr. Sterling's website?

A. No, that's not Dr. Sterling's website. MDCalc is maintained -- I'm not sure exactly maintains it, but it's -- it's some organization that they take well-validated

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scores that are used for prediction models or re-stratification models from many different fields, you know, cardiology, liver disease, you know, oncology, all sorts of different fields. They identify scores that have been well-studied and validated, and then they typically reach out to authors who published them to get their permission to put there formula onto the site and then the -- you know, code it basically to facilitate a centralized resource to -- to -- to help with broad usage of a validated tool. That's usually their process.

Q. Understood. So when you were saying app or website, you meant MDCalc has a website and an app?

A. Yes.

Q. Understood.

A. Yes, yes, yes. Sorry. That was unclear.

MR. VAUGHN: All right. Kathryn, can you drop in the FIB-4 web page for Richard Sterling.

MS. AVILA: Yes. It should be in there now.

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BY MR. VAUGHN:

Q. I'll share the PDF version of this web page. It typically has a picture of him, but you can see down here is this the Richard Sterling you are talking about?

A. Yes.

Q. Okay. And do you see up here at the top where it says, "FIB-4 was developed in patients with HIV and HCV coinfections"?

A. Yes, I see that.

Q. And does that mean that the patients that FIB-4 was developed in had both HIV and HCV?

A. That -- yeah. That appears to be the case based on that sentence.

Q. Is that what "coinfection" means, you have both infections at the same time?

A. Yeah. That typically means you have both infections.

Q. And what is HCV?

A. Yeah. So HCV, that's what I referring to previously. It stands for Hepatitis C virus HCV I think I mentioned earlier that my recollection was it was initially derived in patients with HCV as their

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chronic liver disease. So that's what HCV is.

Q. But in actuality, it's people with HCV and HIV at the same time, correct?

A. Sure. Yeah. I -- yeah. I neglected to recall -- I mean, HIV is not a cause of chronic liver disease, so that's why I emphasize the HCV aspect of it. But yes. Yeah. I agree. It says, it was developed in HCV patients who were co infected with HIV.

Q. Does HIV in impact the blood?

A. It can impact blood counts, yes.

Q. Such as platelets?

A. It primar- -- so I'll caveat this by saying that I'm not an infectious disease doctor with specific expertise in HIV but it primarily impacts white blood cells, in particular CD4 blood positive lymphocytes. That's why you may or may not have heard about CD4 counts, but that's the main thing that is tracked for patients with HIV.

And that's also what's used to define potential aids. Acquired immunodeficiency syndrome, AIDS. That's generally, based on how low the CD4 count gets. So not primary platelet counts being impacted.

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Q. And just to be clear to the jury, HIV is what eventually can turn into AIDS, correct?
A. Yes. So HIV is human immunodeficiency virus. And HIV in many patients, if it's untreated, can progress to AIDS, acquired immunodeficiency syndrome.
Q. And Mr. Roberts did not have HIV or AIDS, correct?
A. Correct. He did not have HIV as far as I know. He did not have Hepatitis C virus.
Q. Okay. And then Dr. Sterling has a section here about what perils, pitfalls, and/or tips do you have for users using the FIB-4?
A. Okay. I see it.
Q. Okay. And he says, "It was developed in a cohort of subjects that did not include the young or very old, so it might not perform as well in those populations, given that the age is the numerator. Furthermore, inclusion of age makes it less reliable to loose -- use longitudinally."
What does -- what does that mean:

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"Less reliable to use longitudinally"?
A. "Longitudinally" refers to just over time.
So I -- I don't know necessarily the full context of what he refers to there. But, you know, if you were to track FIB-4 -- I don't know -- over the course of, like, multiple decades, as someone, you know, progresses into old marriage, perhaps his perception is that it impacts the reliability of it.
Q. And is that because age alone could make your FIB-4 abnormal?
A. Yes. I think I stated that previously that, you know, someone who is very old, just on -- on -- you know, on the basis of age alone, they can have an elevated FIB-4. Yes.
Q. And then up here he notes that FIB-4 between 0 and 2 is mild fibrosis.
Do you agree with that?
A. Sorry. Let me look back at this again. Sorry.
FIB-4 was developed to correlate with Ishak levels.

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Yes. I'm okay with that characterization. Yeah. So they -- they -- it looks like they use a different schema for classifying fibrosis. There's -- I've been referring to something called the METAVIR staging, which goes from 0 to 4. It looks like what he's using is something called the Ishak framework, which ranges from 0 to 6, but it's the same principle that there's progressive fibrosis that you can break into, you know, stages of fibrosis.
Q. But you're saying a FIB-4 score of 0 to 2 is mild fibrosis?
A. Oh, I see.
Q. -- above, correct?
A. No, no, no, no. Let me clarify.
That's not what he's saying there. He's not giving you the interpretations of ranges of the FIB-4 score. He's giving you biopsy pathology stages of fibrosis there.
Q. How do you convert, then, the FIB-4 score to the Ishak levels?
A. So when you asked me to describe the process of how they derived the score, this -- what's being described here is actually

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entirely consistent with what I was describing.
They did biopsies in patients. They've looked at the liver biopsies of patients, and they used this Ishak scoring criterion to determine how much fibrosis there was on the biopsies, and that's what's shown there in the area you have highlighted.
So Ishak levels, Ishak Stage 0 to 2 is mild fibrosis. Ishak stage 3 to 4 is moderate. Ishak Stage 5 to 6 is severe fibrosis/cirrhosis.
So they've gathered that for all the patients in their -- in their study, and then they computed the FIB-4. And they used the distribution of FIB-4 scores and compared those to the biopsy results to identify, among the patients with severe fibrosis and cirrhosis, what were the ranges of FIB-4 scores that would help segregate those individuals, you know, in -- into a category as best as possible. They did the same thing for the mild fibrosis side.
Does that make sense?
Q. Are you saying the 0 to 2 here is not talking about the FIB-4 score?

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A. No. That -- that there is referring to the biopsy fibrosis staging.
Q. And so how do you convert from a FIB-4 score to that?
A. So it might be most clear if you were to literally put numbers into the calculator.
Q. All right.
A. So when you put the numbers into the calculator, you put age, AST, ALT platelet count, it will give you a result. That result is what the FIB-4 score is, and it will give you an interpretation of, you know, which fibrosis stage that patient is likely to have on the basis of their FIB-4 score?
Hopefully, that makes sense.
As I was saying, I mean, there -- there have been different validation studies done in different etiologies of liver disease. So even though it was developed originally in Hepatitis C population with co-infected HIV. It has subsequently been studied specifically in patients with MASLD and MASH in a similar fashion to identify the relevant cutpoints for FIB-4 in those patients. And that's what I'm

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citing in my expert report.
I site, you know, some specific studies that identify those cutpoints and how you can map the FIB-4 score for MASLD MASH patient to the pathology on -- on biopsy.
Q. I'm going to go to the actual web page right now so we can actually use the calculator and see if it's accurate on Dr. Sterling's web page.
A. Sorry. I don't mean to interrupt you, but just to clarify, this is not Dr. Sterling's web page. This is MDCalc. This is the resource that I was ref- -- that I was telling you about that --
Q. Oh, okay.
A. -- that is -- so whenever they -- this is a very, very commonly used application, you know, website for -- for clinicians. His picture is there because they feature the inventor of the tool; and this -- this -- this formula and site is made in his consent and in collaboration with him. But Dr. Sterling does not own MDCalc. There are hundreds and hundreds of prediction scores on this website.
Q. That makes sense. I see -- I see

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the MDCalc at the top. I didn't even realize it was the same web page that you were talking about.
A. This was the --
MS. ROSE: Mr. Vaughn, I'm sorry to interrupt. But if we're going to the -- if you're going to ask questions about this website, I'd like it to be introduced as an exhibit so we have a record of it.
MR. VAUGHN: That was -- that was the exhibit I just introduced. He wanted to do --
MS. ROSE: Oh.
MR. VAUGHN: He wanted to do the calculations, and so I'm using it as a calculator strictly to see if it works. He wanted to see it to do the calculations.
MS. ROSE: Right. Is this a different page than was previously introduced.
MR. VAUGHN: It's the exact same page I just introduced as an exhibit.
MS. ROSE: Oh, okay. Apologies. Apologies.

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MR. VAUGHN: You're okay.
MS. ROSE: It looked like a different page.
MR. VAUGHN: It does look different because when I printed it off, it -- you couldn't see his picture. So it made it look different.
MS. ROSE: Okay. Thanks for the clarification.
MR. VAUGHN: You're fine.
BY MR. VAUGHN:
Q. All right. So in your expert report -- this is page 7, I think is the first time I see you doing the FIB-4 score; is that correct?
A. I --
Q. No. You did some earlier, actually. You do one on page 6 it looks like.
A. Yes, I did.
Q. Okay. And do you know how old he would have been at that time in 2009?
A. Sorry. I'd have to do the math.
So he was 64 when he passed away.
Q. 56 maybe?
A. We can try that.

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Q. Let's see what the numbers come out. So 56 and then his AST at this time was 69, correct?
A. Yes.
Q. ALT was 112. And platelet count was 174.
MS. ROSE: Can I ask a question -- I'm sorry. This is for my own clarification.
MR. VAUGHN: Uh-huh.
MS. ROSE: Have these levels that you're putting it in, are you putting it in for a specific date where the --
MR. VAUGHN: Well, if you go -- correct. If you go to page 6 of his expert report --
MS. ROSE: Okay.
MR. VAUGHN: -- towards the bottom he lists the labs out that he used to determine the FIB-4 score.
MS. ROSE: Thank you. And -- and we've established the age of the patient at this time?
BY MR. VAUGHN:
Q. Take your time, Doctor, and let me

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know what age you think I should be entering here.
A. You're probably close. Well, let's see. So I -- I -- I -- you know, from my recollection, I got it from, like, the clinical notes at the time so -- but I didn't write it down every single time.
So he was 64 when he died in 2020 -- 2020. So how much do I have to subtract from that?
This -- this one -- sorry. I'm just trying to scroll through here. So this was the value from 2009. So 11 minus 6 -- 64 minus 11, I think 53. Try 53. It's either 53 or 54 most likely. Yeah.
Q. Okay. That -- 53 comes out to the number you've got. There you go because you've got a FIB-4 of 199.
So this is the formula you were using to get there, correct?
A. Exactly. So that was the exact process I used. I got his age. I looked at his labs on a particular date. I plugged these into this calculator to get the values, and I wrote that in my expert report.

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Q. Okay. And right before your expert -- sorry. Scratch that.
In your expert report, the preceding paragraph notes that he had elevated liver levels ever since he was a teenager, correct?
A. Yes.
Q. And then it says probably has fatty liver.
My -- is fatty liver more indicative of NAFLD or NASH?
A. So just to -- I think I explained this previously, but just to rehash a little bit, fat in the liver, you'd have to determine why there's fat. The main reasons for fat to be there are either alcohol or obesity.
I think we agreed that he doesn't -- Mr. Roberts doesn't really have any significant, you know, regular alcohol use chronic history. So it doesn't appear to be from alcohol.
So his fat in the liver is almost certainly related to MASLD, but the determination of the MASH part is do we think there's inflammation accompanying the fat in

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the liver.
And so the fact that he had elevated liver numbers, AST to ALT, the transaminases, that is the evidence that there's inflammation happening with the fat because when there's inflammation in the liver, that causes some injury to liver cells.
AST and ALT are enzymes that are present inside liver cells. Inflammation causes injury to liver cells, and those AST and the ALT, they spill out of the cells into the blood.
So whenever we see AST and ALT elevated, that's an indication that something will is causing inflammation and injury to the liver, but it doesn't tell you what. You have to do more investigation to figure out what is the thing that is causing the injury. So you have to rule out Hepatitis C. You ruled out Hepatitis B. You have to rule out alcohol.
If you think it's MASLD or MASH, you have to demonstrate that there's fat in the liver, and you typically look for other metabolic comorbidities, like diabetes, high blood pressure, high cholesterol, and obesity.

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And then you make your assessment through this process of ruling out other explanations for the elevated AST and ALT and then ruling in the likelihood of MASLD.

Q. Can you have elevated AST or ALT without inflammation in the liver?

A. Yes, you can.

Q. And Mr. Roberts had elevated AST and ALT since he was a teenager reportedly, correct?

A. Yes.

Q. Okay.

A. Let me clarify one thing. I apologize, Counselor.

You can have elevated transaminases that separate from inflammation, but that's mostly related to AST. ALT's actually very specific to the liver.

The -- the context there is that AST is also produced in other areas of the body, like in muscle, for example.

So in ALT being elevated is very, very strongly associated with inflammation specifically in the liver. It's really the AST, if that is abnormal, that's not as much of

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a guarantee to be related to the liver.

So I just wanted to clarify that. I apologize.

Q. Thank you. And earlier you were talking about age was a big component of the FIB-4 score, correct?

MS. ROSE: Object to the form.

THE WITNESS: I don't know if I'd say it's a big component, but it is a component of the score.

BY MR. VAUGHN:

Q. Okay. And so if Mr. Roberts would have presented with the exact same labs when he was a teenager, let's say the upper end of being a teenager, 18, his FIB-4 score goes from a 1.99 down to a 0.67, correct?

A. Sure. Yeah. I agree with that.

Q. And is a 0.67 indicative of advanced fibrosis?

A. No. That would essentially exclude advanced fibrosis.

Q. So strictly his age is what is giving that result of fibrosis on the FIB-4 score?

MS. ROSE: Object to the form.

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THE WITNESS: Well, yes. I mean, it's a composite of all the factors you put in.

But I understand what you're saying that the only change you changed was the age, and you see how much the FIB-4 score changes. But in my -- I guess two things that I think are important to highlight are, one, as you stated to me from Dr. Sterling, this was not specifically studied in very young patients; but this also makes clinical sense because I wouldn't expect an 18-year-old to have had sufficient time to develop advanced fibrosis and cirrhosis in the presence of MASH. It takes time to get cirrhosis.

So it's -- it's appropriate in this regard that a very young patient, they have a very, very low probability of having cirrhosis in the setting of chronic liver disease in general.

BY MR. VAUGHN:

Q. But the patient you're talking about, if they had those same labs their entire life, they would eventually show that they have

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fibrosis on the FIB-4 score when they got old enough, correct?

MS. ROSE: Object to the form.

THE WITNESS: Sorry. Clarify that one more time, Counselor.

BY MR. VAUGHN:

Q. So if you have a teenager that has these abnormal labs --

A. Yeah.

Q. -- the FIB-4 score would not show fibrosis, correct?

MS. ROSE: Object to the form.

THE WITNESS: Right. So if you had -- if you put these labs in -- and again, I don't know if you'd really apply this for than 18-year-old.

But if you were to do this and you get this value, this .67 value, I would agree that that would suggest, based on the score, that the patient is unlikely to have advanced fibrosis or cirrhosis, yes.

BY MR. VAUGHN:

Q. And so changing only the age --

A. Uh-huh.

Q. -- the 53 gets you to 1.99.

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So this is really just looking at age as a function of fibrosis, correct?
MS. ROSE: Object to the form.
THE WITNESS: No, it's not because those -- if you were to take -- if you were to put in, you know, normal AST and ALT and normal platelet values and then do the same thing with age, you would not see the same thing.
So I mean, if you were to change the AST here to, I don't know, 23 and the ALT to 25 or something, which are normal values, and give, you know, the platelet count of 230, which are very, very normal range values for an individual, I'd expect you'd have a low FIB-4.
So it's not -- it's the entire score. You have to interpret all the inputs together.
It -- this makes perfect clinical sense that somebody with those labs, if -- if, in fact, someone went from 18 years old with an AST and ALT that were chronically elevated in the 60-to-100 range, if they had those labs from age 18

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to age 53, they would, in fact, have a very high likelihood of having cirrhosis because that chronic liver disease had been present for a long enough amount of time to progress through the fibrosis stages. And that's what this risk score is -- is communicating.
That's the main reason why age is in this is because you're more than likely to have had sufficient time to have developed cirrhosis, you know, if -- if you -- if you're older and if you've had a chronic liver disease for a longer period of time.
So to me, it just feels appropriate, what we're seeing from the score.
BY MR. VAUGHN:
Q. And so the FIB-4 index assumes that your fibrosis is going to get worse over time, correct?
MS. ROSE: Object to the form.
THE WITNESS: I mean, the FIB-4 score, you know, we apply it at a data point in time to rule in the likelihood

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that someone has cirrhosis or not so we can figure out the next best step and management for that patient, which oftentimes may involve further testing to confirm or deny a diagnosis of cirrhosis.
But yes, I think the score -- this score and -- and other types of scores like this rely on the assumption that chronic liver disease takes time to cause injury and scarring in the liver, and you have to progress through the stages. That's just part of the underlying understood physiology of -- pathophysiology of how cirrhosis develops. You progress through fibrosis stages to get there, and generally that takes time.
BY MR. VAUGHN:
Q. And so that -- I put in age 30 now.
So even if he was age 30, he would just be a 1.12 at this time on the FIB-4?
A. I agree. That's what it says.
Q. Okay. If -- and if he goes up to age 40, he's now at 1.5?
A. Yeah.
Q. And at age 50, now he hits the

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1.87.
So at age 50 is when you would think he now has fibrosis; is that correct?
A. Well, like I said, fibrosis it progresses through stages. I mean, he likely had more mild fibrosis earlier in his life. And at this point, you know, based on the hypothetical scenarios you're putting into the calculator now, which currently says age 50, he's in that indeterminate range where he would neat further evaluation.
We don't know exactly how much scar he has in his liver based on these hypothetical parameters. He would need further investigation. But we don't have confidence to say that he definitely doesn't have advanced fibrosis or cirrhosis.
Q. And we don't have enough information here to say that he definitely does have fibrosis either, correct?
A. He very likely has fibrosis, but we don't have enough information here to say that he very likely had cirrhosis.
Q. You can say -- okay. So if I take him back to, let's say, 40 years old, and we

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now get a FIB-4 score 1.5, is it likely that he has fibrosis at that time?
A. Yes, it's likely that the patient has fibrosis. And so actually, if you look at the interpretation just below the 1.50 --
Q. Uh-huh.
A. -- you see that the approximate fibrosis stage is Ishak 2 to 3. And so that is what corresponds to what you were pointing to previously about 0 to 2, 3 to 4, 5 to 6. That's what you would expect to see.
If you were to do a biopsy in this hypothetical patient, you would expect that they would probably have fibrosis somewhere in the intermediate range.
Q. Okay. So when he was 18, the same labs, would he have fibrosis then based on your assessment?
A. Yeah. So I mean, based on FIB-4 alone, again, I -- you know, we -- we don't rely on FIB-4 exclusively. We look at the composite of multiple things.
But so with that stated, if I were to just look at the FIB-4 here, he's likely to have, you know, minimal to no fibrosis. I

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mean, so the estimate there is Ishak 0 to 1. So zero would be no fibrosis. One would be mild fibrosis. So he might have had some very mild fibrosis at that time. That's what the FIB-4 score would be telling you based on that -- those values.
Q. All right. Let's go back to Exhibit 1, your expert report.
A. Okay.
Q. Give me one second. Okay.
On page 7 of your expert report, and so when we were looking earlier at 2009, that platelet count -- actually page 74.
MR. VAUGHN: Kathryn, can you go ahead and drop that in as the Exhibit, the 2009 labs.
MS. AVILA: Okay. They should be in there now.
BY MR. VAUGHN:
Q. Doctor, I have that pulled up on the share screen. So these are the August 19th, 2009, labs.
MR. VAUGHN: I believe this is Exhibit 7.
MS. ROSE: I think it's Exhibit 8.

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MR. VAUGHN: You're right. Exhibit 8. Thank you, Nina.
(Whereupon, Exhibit 8, Medical Record, Bates labeled Restricted Confidential Information GRobertsJr-CA-000659, was marked for identification.)
BY MR. VAUGHN:
Q. Do you see this platelet count is 174, and the doctor's actually circled the platelet count?
Does that mean the doctor is looking specifically to see what his platelet count is?
MS. ROSE: Object to the form.
THE WITNESS: I -- I don't know who circled that or what -- you know, what they would have been thinking when circling it. So it's impossible for me to say.
BY MR. VAUGHN:
Q. Understood. Is that a normal platelet count, in your opinion?
A. It is on the very low end of normal.

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Q. And the reference range for this lab for platelets, the bottom end range is 140, correct?
A. That's what the reference range states on the lab report, yes.
Q. Okay. But you use a reference range of 150, correct?
A. Yeah. Yeah. As I stated previously, you know, we regard an abnormally low platelet count to be less than 150; but as I said also, oftentimes, the trend is also important in looking where the platelet baseline was and where it's been going.
Q. And let's go back to your expert report, page 7, you note in 2011 that Mr. Roberts had GERD and was managed with a PPI, proton-pump inhibitor.
Is there any relevance to that, in your opinion, to his case?
A. No. I don't -- I don't rely on anything with proton-pump inhibitors to inform my -- my primary opinions.
Q. So were you just kind of going through his medical history here?
A. I think so. Yeah. I think I -- I

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must have just written that down when I was looking through the note. I think I was trying to be comprehensive in -- in accumulating the different comorbidities that he had across the medical record. And so if there was a new diagnosis that was mentioned, I made an effort to write that in just for completeness.

So, you know, it's -- it's relevant to know if someone has GERD because it's another thing that is associated with obesity. So, you know, I don't think it's necessarily directly relevant to him developing hepatocellular carcinoma, but it's important in this context to understand that the burden of comorbidity that Mr. Roberts had that was likely associated with his degree of obesity.

Q. Okay. So you didn't need to do any research into proton-pump inhibitors, correct?

A. For the purpose of this case, no, I didn't -- I didn't look in detail at relevance of a proton-pump inhibitor for this case.

Q. And then the next FIB-4 you did, it looks like was at this November 4th, 2015, with the following labs: AST 65, ALT 78, and platelet count 137.

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And you're diagnosing him yourself now as thrombocytopenic, correct?

A. Correct, yes.

Q. Okay.

MR. VAUGHN: And, Kathryn, can we go ahead and do those labs now. This will be Exhibit 9.

(Whereupon, Exhibit 9, Medical Record, Bates labeled Restricted Confidential Information GRobertsJr-AMG-000051 through Restricted Confidential Information GRobertsJr-AMG-000053, was marked for identification.)

MS. AVILA: Yes. It should be in there now.

BY MR. VAUGHN:

Q. Doctor, do you see here, August 19th, 2009.

Oh, did I do the wrong one?

A. Yeah.

Q. I totally did. Sorry about that.

A. That's all right.

Q. November 4th, 2015, CBC and the platelet count is now 137.

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And do you see how this lab, the low end of the reference range has now dropped to 130 as opposed to 140?

A. Yes, I see that.

Q. And no diagnosis was given for thrombocytopenia at this time by his doctors; is that correct?

A. I don't think -- I don't recall his -- I think Dr. Sanders had been ordering these labs, from my recollection, because I'm looking at my report as well.

I don't think at this time the platelet count was discussed with him.

Q. Were you aware when you were writing your expert report that the reference range for this lab was 130 for the low end?

A. Yeah. I did see that.

Q. And you didn't mention -- excuse me.

And you didn't mention in your expert report what the reference ranges were for the labs, correct?

A. No, I didn't, but I have already provided you with the context that in the field of hepatology and informed by, you know,

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multiple hepatology guidelines, the platelet count of less than 150 interpreted in the proper context has significance with respect to cirrhosis and elevated portal pressures. And that's why I specifically noted in my report in the parenthetical that thrombocytopenia is defined by platelets less than 150.

So I -- I took the time to write that out because I acknowledge that the reference range here would make that appear with -- within the normal range of this lab. It wouldn't get flagged as being low. But to me as a hepatologist, that's clearly abnormal.

Q. And you're using the low platelet count to support your opinion that he had portal hypertension at this time?

MS. ROSE: Object to the form.

THE WITNESS: It's -- it would be consistent with him developing portal hypertension. Yes.

Again, I don't rely on just one data point to make these determinations. I looked at multiple data points wherever possible.

So he doesn't have a CT scan, for

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instance, at that particular time point. He gets one five months later, which does corroborate that he does have portal hypertension.

So in my view, I'm concerned that this patient is developing portal hypertension and may already have, likely already has portal hypertension. But I would have done more investigation. If I was his treating physician at that time, I would have tried to do more investigation to confirm that.

BY MR. VAUGHN:

Q. And -- and in writing your report and coming to your expert opinion, did you into any other patient-specific factors specific to Mr. Roberts that could have explained this drop in platelet counts?

A. I did.

MS. ROSE: Object to the form.

THE WITNESS: I'm sorry.

MS. ROSE: No that's okay. Go ahead.

THE WITNESS: So yes, I did. So I considered some of the factors that I've

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already mentioned to you.

Did he have his spleen removed? He did not.

Did he have immune thrombocytopenic purpura, ITP? He did not.

I've looked at medication-related causes. I remember specifically looking through Dr. Sanders' medication list. And because there are some medications that can sometimes cause low platelets, I did not identify any obvious offenders that would -- that be associated with a low platelet count.

And then I looked at the overall trend as well because there are some patients that have -- you know, there -- there are different types of inborn kind of mutagenic base conditions where they always have a low platelet count, but that's clearly not the case for Mr. Roberts either because his platelet count was normal. And then it downtrended to the point where it was abnormal.

And so I considered all those factors as I would for any patient that I

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take care of. I think very carefully about the platelet count in particular because I know that you have to be mindful of interpreting that in the context when you compute a FIB-4.

And as I mentioned, just to bring back one specific point, a lot of the veterans I had taken care of, alcohol is, unfortunately, a big problem. And if patients are heavily drinking alcohol, that can suppress the bone marrow, that can suppress the platelet count.

So yes. I consider that too. And as we've already talked about, Mr. Roberts didn't seem to be a heavy drinker. You know, there's no consistent mention of him heavily using alcohol.

There are other features on his lab tests that make significant alcohol use unlikely too, but yes, I thought about all those different things when I was interpreting his platelet count.

BY MR. VAUGHN:

Q. What medications are you aware of that can decrease someone's platelet count?

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A. There are certain antibiotics. For instance, you know, one particular one is bactrim or trimethoprim, sulfamethoxazole that's associated with low platelet counts.

There are some immunomodulator medications that are -- that are known to suppress the platelet count and impact the CBC generally. There are things like ASO diaphragms. There's a range of different ones, but the medications that he was on at the time, which I -- I can't exhaustively tell you the list off the top of my head, but I did review the medications that he was taking to see if they were plausibly linked to his platelet count being low.

Q. When you say you reviewed the medications that he was taking to see if there was a link -- plausible link to his platelet count being low, were you just going off of the current knowledge you had of what medications could lower someone's platelets?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I'd say that my current knowledge is informed by the experience using medications and taking

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care of patients who are on many of these very common medications. And that's usually based on a review of a resource such as UpToDate, which is a -- a medical resource where you can look up a wide variety things that are pertinent to -- to practitioners across lots of different disciplines, but it includes very detailed summaries of medication profiles, dosing ranges, indications, adverse effects, contraindications, things like this.

You know, and that oftentimes includes, you know, for medications, what is the -- the -- what proportion of patients may have issues with blood counts or -- or -- you know, thrombocytopenia things of that nature.

So -- so yes, it's based on my knowledge, but my knowledge is informed by, you know, years of that kind of research and interaction with the medical literature and medical resources.

BY MR. VAUGHN:

Q. As you were drafting your expert report for Mr. -- scratch that.

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As you were drafting your expert report, did you run each of Mr. Roberts' medications through UpToDate to see if they could have an impact on his platelets?

A. I probably did not run each one through UpToDate. I -- I -- I recall running some of them, the ones that I may have had lesser certainty about.

But as I said, a lot of the medications he was on are -- are ones that are very commonly encountered in the setting of patients with MASH -- MASLD and MASH, and diabetes medications, medications for high blood pressure, et cetera.

So you know, I -- I relied on my existing familiarity in some sense -- in some sense to -- to make that adjudication. But additionally, like I said, I never in isolation looked at the platelet count. I'm looking at the platelet count in the context of the trend and other corroborating information that help me understand why the platelet count might be dropping. So that's -- that's the way I approached my review of this area of his record.

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Q. What relevance would there be --

MS. ROSE: Mr. Vaughn?

MR. VAUGHN: Yeah.

MS. ROSE: Sorry. I don't want to interrupt you while you're --

MR. VAUGHN: It's okay.

MS. ROSE: -- on a role. But I just wanted to note it's been about an hour so if you --

MR. VAUGHN: Oh. I'll wrap up very quickly.

MS. ROSE: Okay. Great.

BY MR. VAUGHN:

Q. If his platelet were to go up at some point later, what would that indicate to you?

A. Well, it's -- it's hard to -- to know. I mean, there's a lot of potential reasons why the platelet count could go up, and so it would be very dependent on the particular context in which it might be elevated. So it's hard to answer that specific hypothetical.

I mean, you know, for instance, someone could be actively infected, and, you know, they've been to a hospital and their

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platelet count is low and they get a platelet transfusion. So there's a very specific context understanding what's happening to the platelet count in a patient like that.

So yeah. So it's hard to say without kind of more specific details of what a hypothetical might be, but there are so many things that can affect platelet count.

Q. So just specific to Mr. Roberts, no other facts change, but let's say later on his platelet count returns to normal.

Would that be indicative of anything to you?

MS. ROSE: Objection to form. Incomplete hypothetical.

THE WITNESS: Yeah. That's right. I agree. It's a tough hypothetical to answer.

But platelet counts fluctuate, and this is why I keep emphasizing the trend. If I were to check someone's platelet count in the morning and then check it the next day, it's not going to be the exact same value. These are always in fluctuation.

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So the trend in the platelet count is also important to -- to understand as well as the -- the milieu of other clinical data, imaging data in the patient context, whether or not chronic liver disease is there and -- and what the pretest probability is for cirrhosis.

So -- so I'm not overly fixated on the platelet count alone. I'm -- I'm looking at the platelet count and its trend in the context of the entire clinical picture.

I understand that the platelet count can fluctuate up and down, but my concern in his history is that his platelet count was trending downwards, and there was really no other alternate explanation besides cirrhosis and portal hypertension, which is, I think, substantiated by multiple other lines of evidence.

BY MR. VAUGHN:

Q. After this date 11/4/2015, are you aware of his platelets going back up ever?

A. Let's see. I don't know if I

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exhaustively listed all of his platelet counts. I -- I couldn't -- excuse me -- I couldn't tell you concretely yes or no. I think I may have picked a couple other time points to look at.

Q. Did you only list his only low platelet counts in your report?

MS. ROSE: Object to the form.

THE WITNESS: Well, clearly not because we already reviewed some of the -- the normal range platelet counts from earlier in his medical history.

BY MR. VAUGHN:

Q. After the first one that was normal, once it started trending downwards, did you list any of them that were normal?

MS. ROSE: Object to the form.

THE WITNESS: I would have to review briefly here. I'll take a look.

MR. VAUGHN: We can take a break now, Nina.

MS. ROSE: Oh, sure. Do you want to take the break right now?

MR. VAUGHN: Yeah. Now works.

THE VIDEOGRAPHER: Off the record, 2:32.

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(Whereupon, a break was taken.)

THE VIDEOGRAPHER: We are back on the record at 2:45.

BY MR. VAUGHN:

Q. All right. Doctor, I'm going to admit Exhibit 9.

MR. VAUGHN: Kathryn can, you drop the 2018 adverse effects of proton-pump inhibitors on platelet count.

MS. AVILA: Yes. And I think it's Exhibit 10.

MR. VAUGHN: Exhibit 10. Thank you.

(Whereupon, Exhibit 10, Case report entitled, "Adverse Effects of Proton Pump Inhibitors on Platelet Count: A Case Report and Review of the Literature," by Subhajit Mukherjee, et al., was marked for identification.)

BY MR. VAUGHN:

Q. Doctor, have you seen this case report before?

A. I don't think so, not to my recollection.

Q. Okay. And do you see here it was

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published in 2018?

I just want --

A. Yes, I see that.

Q. Okay. I just want to take you to the third page where they note, "Based on the findings from these case reports and from our observation, it appears that PPIs can cause thrombocytopenia."

Did I read that correctly?

A. Yes. You read that correctly.

Q. Okay. And as you were forming your opinions in this case, were you aware that PPIs could cause thrombocytopenia?

MS. ROSE: Object to the form.

THE WITNESS: So you're showing me what appears to be a case series, which I -- I think I articulated previously are not very strong -- sorry. It's a case report, not a case series.

This is based on -- this is one case of a 35-year-old female who came in with abdominal pain with a past history of heartburn and treated with PPI.

It's very hard to make an inference about one -- from a case report or even a

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case series, for that matter, what is the true causal association between something like a PPI and an outcome.

This is not robust evidence in my view, and I'll just say that as a gastroenterology, you know, I -- I prescribe PPIs very frequently. Many of my patients with MASLD and MASH are on PPIs. Probably the majority of them are on PPIs, and I can't think of a single case personally where low platelets are attributed to PPIs in this patient cohort.

But PPIs more generally are very commonly falsely associated with different medical end points because they're so commonly used for a variety of different conditions.

So, you know, I can't comment to the -- the details of all the different case reports that they may be referencing here to form some assessment of a -- a case series, but they -- they report just a small number of case reports that demonstrate this.

But like I said, you know, case

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reports are not associational studies. They are not estimating -- they're not performing any analytical statistical analysis to estimate what is the risk of low platelet counts with -- with PPI exposure.

So it's really hard to translate this to -- to Mr. Roberts and say with any degree of certainty that PPIs were -- would be related to his platelet count. Though in my view, it's almost certainly unrelated.

BY MR. VAUGHN:

Q. And you didn't do any research on PPIs causing low platelet counts, correct?

MS. ROSE: Object to the form.

THE WITNESS: So in the course of this particular case, no, I didn't explore any specific associations about PPIs and low platelet counts for the context of this case, but I am familiar broadly with a lot of the PPI-related liter- -- literature as pertaining to a wide variety of clinical outcomes.

And so I alluded to this for the

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very specific reason that PPIs are oftentimes falsely associated with sometimes very serious clinical end points that are later found to be totally irrelevant and unsubstantiated.

If I may just give a very quick example to drive this point home. There were some very big headlines -- media headlines that came out -- I don't know. It was quite a few years ago now that PPIs cause heart attacks, and those were based on associational studies where patients, you know, presenting with chest discomfort, you know, who were then started on proton-pump inhibitors presuming that it was related to gastric reflux.

The -- the association is in those studies were that PPIs were then associated with increased risk of having a heart attack shortly after a PPI was started.

Very well-controlled studies that subsequently came out that accounted for confounders of coronary artery disease

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demonstrated that the chest discomfort was not from the reflux. It was from heart disease. And the patient's were had very high risk of having an impending heart attack, but PPIs were just started because some clinician thought, okay, maybe this PPI will treat the chest discomfort. So you get this false association between PPIs and heart attacks that's not real.

So I -- I highlight that because there are lots of -- you'll find lots of case reports and series alleging that PPIs are linked with all sorts of things.

You know, this -- I'm not sure what was going on with this particular patient, you know, when she -- what symptoms she was having and the PPI may have been started for some generic reason when, in fact, something else was going on that was driving the low platelets. But there's no way to say without, you know, a high quality analytic study.

So I don't view this to be very strong evidence. And again, you know, in the aggregate of how many patients are on

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PPIs, I would expect that there would be very, very strong evidence if this was a real causal association.
BY MR. VAUGHN:
Q. Are you familiar with the term de- -- scratch that. Sorry.
Are you familiar with the term "dechallenge"?
A. Sorry. Dechallenge?
Q. Uh-huh.
A. I -- I may be. When you -- you take someone off a medication, is that what you're referring to, when you stop a medication?
Q. Right?
A. Yes, yes. I'm familiar with that term.
Q. Can you explain what a dechallenge is?
A. Yeah. If I'm understanding what you're referring to correctly, you know, someone who is on the medication, and then you take them off the medication and observe.
Is that what you're referring to?
Q. It is what I'm referring to.

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A. Okay.
Q. Is -- are dechallenges strong evidence?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. It really depends on the context in which it's being used. I mean, I think if you, you know, do dechallenge -- dechallenges in the setting of a very-well controlled study with a sufficient sample size looking for some particular outcome, then it may be relevant.
But it entirely depends on the research question and how the de- -- dechallenge is -- is actually administered and, you know, what the rigor of the surrounding methodology in the study is.
So it's hard to answer precisely, but there are many other considerations besides a dechallenge itself that, you know, might be relevant to know.
BY MR. VAUGHN:
Q. Does a dechallenge make a case study stronger?
A. Potentially, you know, in a very

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limited sense. I think if somebody is dechallenged and rechallenged, you -- the issue is that you would also know what other relevant factors may also be changing in a patient.
So, you know, if -- I'm trying to look at this figure to understand -- just give me a second to look at this Figure 1 to try to catch up where you're going with this.
Yeah. So this patient, it looks like they're on a PPI. It is then discontinued. They are restarted on the PPI. It is then discontinued.
So there's a -- there was, it looks like two dechallenges, in this case report.
Is that what you're referring to?
Q. Yeah. And you mentioned a rechallenge.
What does that mean?
What's a "rechallenge"?
A. Sorry. A rechallenge, what I mean there is if someone is given a medication again.
Q. And the side effects happen again?
MS. ROSE: Object to the form.
THE WITNESS: Sorry. The

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rechallenge just refers to reintroducing whatever the exposure is.
BY MR. VAUGHN:
Q. And they're -- with the rechallenge, though, are they looking to see if the side effect happens again when the exposure is presented again?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. So again, in the setting of a case report, this is not being done in an interventional way. You know, they're -- it's not like she was part of a study where they were going to give her a PPI, observe her, then dechallenge her, observe her, rechallenge her, observe her. That's not the point of this.
It -- my understanding -- most of the time in case reports, and I can read this in more detail to confirm this, but the patient happened to have been given a PPI. It happened to have been stopped. It happened to have been restarted. And they're reporting what the observations were.

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And it's an important distinction because it's not being done in an experimental setting. She's not being given this and taken off of it while controlling for myriad other factors that may or may not be relevant.

So it's -- it's not -- so -- so even using the term like "dechallenge" and "rechallenge," I don't want to imply that this is being done in an interventional sense because I don't think that's what this is -- this case report is stating.

BY MR. VAUGHN:

Q. Are you familiar with the term "double dechallenge"?

A. I don't know if I've used that term previously, but I can infer that you're referring to someone who has been dechallenged twice.

Q. Uh-huh. Does that provide stronger evidence of a causal link?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I think my response is similar, where if it's not done in a very controlled setting in the

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context of some sort of interventional study or very well-adjusted study that is, you know, really designed appropriately to look for potential causal associations, then no. I mean, it doesn't -- it's not -- I -- I wouldn't be able to translate that to a causal association.

It -- you know, all this -- my same previous points, I think, still apply. You're not controlling other aspects of the situation. I don't know what other co-associated factors may have also changed, you know, at the time that a PPI may have been reintroduced, for instance.

BY MR. VAUGHN:

Q. Okay. And the authors here note that thrombocytopenia attributed to use of PPIs has been described in a few case reports and a retrospective study.

Are you aware of what retrospective study they're referencing here?

A. I'd have to see what the citation is.

Q. Okay.

A. If you could maybe show that to me,

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I could -- I could tell you if I've seen it or not.

Q. I don't know what the citation is either.

A. Okay.

Q. I didn't know you were aware of a retrospective study that looked into PPI use being associated with thrombocytopenia before you authored your expert report.

MS. ROSE: Object to the form.

THE WITNESS: And yeah. I'd really have to know what they're referring to. They don't seem to offer the citation, so I -- I can't really speak to the validity or even the presence of it if it's not referenced or cited.

BY MR. VAUGHN:

Q. And you didn't do any searching for PPIs being linked to thrombocytopenia, correct?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. Like I said, in the context of this specific case, I did not do any dedicated searches for PPI and thrombocytopenia for this.

But again, I have to emphasize that

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I'm not really relying exclusively on the platelet count to make my determinations of, you know, presence or absence of cirrhosis in Mr. Roberts' case. It's myriad factors that I'm using as a composite to arrive at a conclusion.

BY MR. VAUGHN:

Q. And you agree that Mr. Roberts' platelet count dropped after he was started on a PPI, correct?

A. Hold on. Let me take a look at my report for a moment. Let's see.

So I think the problem with the assertion that I think you're -- you're implying was that Mr. Roberts is on a PPI for quite some time. You know, if you're trying to impute that or suggest that there's a relationship between an exposure and an outcome, obviously the temporal association is relevant.

I would agree that if you start someone on a medication and you very quickly see some relevant change in their labs or -- or symptoms, then you -- you dechallenge them and you rechallenge them, and you see that there is

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a very close approximation, that is -- you know, that's more evidence than not. I still don't think it's a well-established causal association, but that's not what we're observing in Mr. Roberts. Mr. Roberts was diagnosed with GERD in 2011 and started on a PPI in 2011.

So, you know, this case report here is basically showing that, you know, in this patient she was started on a PPI -- sorry. I'll look at the -- the time course again here.

And it's over the course of a shorter window of time, you know, when -- when this patient developed a low platelet count and in a much more severe thrombocytopenia than was observed in Mr. Roberts, but these are really being studied over the course of less than a year.

Mr. Roberts had been exposed to a PPI for, you know, four years, you know, four years really prior to developing overt thrombocytopenia. So it's -- it's really not plausibly linked in my view to being causal of his low platelet count, especially in light of evidence of he had portal hypertension, which

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fits directly with his low platelet count.

So it's a much, much more likely explanation for what's going on with Mr. Roberts than what I think you might be suggesting.

Q. Are you aware of any platelet counts from 2011 when he started the PPI to November 4th, 2015?

A. I don't think I noted those in my -- in my report. So I'm not sure. I can't confirm or deny if there are platelet counts checked in those windows.

It looks like the most recently available platelet count prior was the value from 2009. From late 2009 it was -- it was 174. I'm not certain if there's another one available from this record between 2011 and 2015.

Q. And so we can't tell when his platelets dropped after starting the PPI, correct?

A. Yeah. I think that's fair to say. And based on, you know, my understanding of the record, I don't know if his platelets really tracked so closely.

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But again, I think the -- this case report -- the degree of thrombocytopenia was extremely notable. It dropped, you know, very close to zero. You know, it nattered very low on this -- this chart. That's not really the -- the pattern for Mr. Roberts. It was more of a gradual decline.

Q. And Mr. Roberts only had very mild thrombocytopenia, correct?

MS. ROSE: Object to the form.

THE WITNESS: I wouldn't -- I wouldn't say that. I'm just saying that the cadence and the pattern that's sergeant in this report that you're showing me is where someone goes from a very normal robust platelet count to practically zero. It's a very extreme oscillation in the platelet count.

Whereas, Mr. Roberts, if you were to map out his platelet count, it seems to be dropping gradually, trending downward gradually over time, which is very consistent and expected with the -- the tempo of cirrhosis.

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BY MR. VAUGHN:

Q. What is a very normal platelet count?

A. So a normal platelet count is over 150. When I say that -- I guess when I say very normal, it's -- it's very close to the -- the center of the normal range.

Q. And what is that?

A. So, you know, a normal range is typically, you know, 150 to 400. So someone that's in, you know, the mid-200s is -- that's -- that's a very normal platelet count.

Q. Okay. So Mr. Roberts starting off at 175 is starting off on the lower end of normal?

A. Well, I don't --

MS. ROSE: Object to the form.

THE WITNESS: Sorry.

Yeah. I don't know what his -- unfortunately, his platelet counts are not, you know, recorded earlier in his adulthood. So I don't actually know where, you know, for instance, where things started out when he was in his teens and 20s and 30s. We just don't have

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records, unfortunately.
All I can see is where he is starting out is in the normal range in his records. You know, 2009 I think is the first one that I -- I -- I noted when it was 174. So he's normal there, but he's already on the lower end of the normal range. I would acknowledge that.
BY MR. VAUGHN:
Q. And back to the study we were looking at, this specific patient they note, "Thrombocytopenia immediately developed after initiation of PPI on two separation occasions and resolved after it's discontinuation."
Do you read that to be a double dechallenge with a rechallenge?
A. Yeah. I think, based on the definition of double dechallenge that, you know, you gave me and we discussed, that's what it sounds like, yeah. They took the patient off the medication on two occasions, and they noted what the platelet counts were.
Q. And so was one of your issues with the PPI being associated with Mr. Roberts' thrombocytopenia is that gap -- the temporality

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gap of it starting in 2011 and him presenting with what you call thrombocytopenia in 2015?
MS. ROSE: Object to the form.
THE WITNESS: That's -- I mean, I ' just highlighting that one issue because the case report you're showing me shows very extreme changes over a short time period with this PPI exposure. And I don't think we have any evidence of that in Mr. Roberts. You know, he never got his platelet count close to zero.
And, you know -- but moreover, I think that -- again, I'm considering other factors beyond the platelet count to try to understand why it is that it's gradually downtrending in his -- in his case.
And, you know, everything I'm reviewing in his history, there's very strong evidence that he has had progressive fibrosis and cirrhosis and then development of portal hypertension, which is the most likely explanation for his declining platelet count and one that is very typical of patients that I see all

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the time in my practice who develop cirrhosis.
BY MR. VAUGHN:
Q. And so because portal hypertension is the most likely explanation for most patients, did you not feel it was necessary to do research into other causes of thrombocytopenia specific to Mr. Roberts?
MS. ROSE: Object to the form.
THE WITNESS: No. I wouldn't say that. I -- you know, I -- I -- I'd be interested certainly to review, you know, in more detail relevant literature pertaining to proton-pump inhibitors and thrombocytopenia to see what the strength of the evidence. And I always reserve my right -- right to revise any aspect of my opinion.
But what you're showing me is not compelling evidence for the reasons that I've stated. It's a case report, and they reference other -- other case reports to construct an idea of a case series, but these are not controlled, you know, analytic studies to -- that are capable of

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demonstrating, you know, statistical associations between an exposure and an outcome. They're just case reports.
So I don't view them to be strong evidence. You know, they're -- they're and interesting thing that may be the basis for -- for future research in an -- in an observational study or a trial setting or whatever it might be. But I don't view that to be well-founded causal associations that are demonstrated to be relevant here.
So I -- I rely on the corpus of medical literature that is very well-established, you know, from a cirrhosis standpoint that I think is relevant here that demonstrates that this is the expected trajectory of platelet counts in patients with preexisting chronic liver disease who develop cirrhosis and progress to developing portal hypertension.
BY MR. VAUGHN:
Q. You mentioned earlier some other drugs that could cause thrombocytopenia.

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Is -- are diuretics a class of drugs that can cause thrombocytopenia?
A. I am not a hundred percent sure. It's possible, I mean depending on the diuretics. There's a lot of different diuretics that are used. So I don't immediately know -- I don't immediately know off the top of my head if, you know, if there might be one that is associated with thrombocytopenia to a significant degree.
Q. And you didn't do any research in your -- scratch that.
And you didn't do any research in drafting your expert opinion to see if diuretics were a cause of thrombocytopenia, correct?
A. I didn't do any specific research for this expert report specifically looking at the association between diuretics and thrombocytopenia; but, you know, I'd say that in the course of my practice, you know, we use diuretics very frequently in patients with liver disease. And so I count- -- encounter them all the time, and it's certainly not something that we see in routine practice.

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There -- you know, I don't discount that there might be some exceptional cases where there might be associations or where -- where it's posited as an explanation for extreme thrombocytopenia in some patients, but I don't know it to be a strong association in my clinical practice.
Q. Okay. And did you review Mr. Roberts' pharmacy records to see if any medications were changed right before his platelets dropped for the first time?
A. Yeah. I mean, I did review -- you know, every time he saw a clinician, I did look through his medical record to -- to try to keep track of big changes; but I couldn't immediately tell you off the top of my head what specific changes might have been made antecedent to, you know, his platelet count in 20- -- 2009 or antecedent to 2015 off the top of my head.
Q. Okay.
MR. VAUGHN: Kathryn, can you drop in the pharmacy records as exhibit, I believe, 11.

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(Whereupon, Exhibit 11, North Baldwin Pharmacy, pharmacy record for Gaston J. Roberts, Jr., was marked for identification.)
MS. AVILA: Yes. They are in there now.
BY MR. VAUGHN:
Q. Doctor, do you agree that first lab where he had lower platelets?
It was 1/4/2015?
A. Let me see. Yes, I agree with that. That's the first time that he had thrombo- -- thrombocytopenia by my definition, yes.
Q. I'm on page 2 here. All right.
So on 7/27/2015, we see he's taking Valsartan, 320 milligrams, correct?
A. Yes. I see that.
Q. Okay. And then on 10/8/2015, do you see where they transitioned him now to Valsartan HCTZ?
A. Yeah.
Q. Okay. And so this would have been approximately two to three weeks before these labs were drawn, correct?

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A. Yes. I would agree with that.
Q. Okay. And what does the "HCTZ" stand for in Valsartan?
A. That's hydro- --
Q. Sorry.
A. It's -- it's hydrochlorothiazide, which is a diuretic medication.
Q. Okay. Did you do any research into hydrochlorothiazide and thrombocytopenia when coming to your expert opinion?
A. No, I did not specifically look at that association.
MR. VAUGHN: All right. Kathryn, can we do the 1986 study on hydrochlorothiazide-induced thrombocytopenia.
MS. AVILA: Yes. And that's Exhibit 12.
(Whereupon, Exhibit 12, Study Entitled, "Hydrochlorothiazide-Induced Thrombocytopenic Purpura," by Kingsley C. Okafor, et al., was marked for identification.)
BY MR. VAUGHN:
Q. Here we go. 1986

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Hydrochlorothiazide-induced -- what is -- what is -- what is this word?
Thrombocytopenic purpura, is that how you say it?
A. Yeah. Thrombocytopenic purpura.
Q. What does that mean?
A. Well, I have to say in 1986, this is quite a long time ago; and sometimes these terms may have been used differently in that era to be quite frank.
The purpura generally refers to a bruising that you might see on the skin related to very, very low platelet counts. You know, because platelets are important to, you know, to help with stopping bleeding. They're important for forming clots.
And so if you have extremely low platelet counts, you can sometimes she some of this spontaneous bruising. That -- that's how it's commonly used currently. I'm not sure back in 1986 if that might have had a slightly different connotation.
Q. Okay. And so back in 1986, they identified that the drug, which is hydrochlorothiazide, was discontinued. Two

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weeks later the patient's symptoms resolved completely, and his platelet count returned to normal.
That's again describing a dechallenge, correct?
MS. ROSE: Object to the form.
THE WITNESS: Let me take a look at that.
So the drug was discontinued. Two weeks later the platelet count was returned to normal. Let's see.
Yeah. I guess -- yep. True. They took him off the medication, which if you want to define that as a dechallenge, then that appears to be what they did, yes.
BY MR. VAUGHN:
Q. And then they start talking about thiazide diuretics.
HCTZ would qualify as a thiazide diuretic, correct?
A. Yes.
Q. And it says, "Thiazide diuretics have been shown to induce thrombocytopenic purpura." And that these authors found 26 to 71 patients -- percent of patients receiving

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oral diuretics had platelet counts less than 100,000; is that correct?
MS. ROSE: Object to the form.
THE WITNESS: I mean, I agree that's what the sentence says. That's what the -- yeah. You read it correctly.
BY MR. VAUGHN:
Q. And then it talks about when there is thrombocytopenia due to a thiazide diuretic, it's usually a gradual onset, mild rather than severe, and the decrease in platelet count occurs after several days of therapy, correct?
A. Yes.
Q. And would you agree that several days after Mr. Roberts was started on HCTZ, he had a mild drop in his platelet count?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. So based on the medication logs you showed me for the timing of when the HCTZ was added to his Valsartan, yeah. His platelet count was a little bit lower on the subsequent check.
BY MR. VAUGHN:
Q. And again, a dechallenge would be if they then took him off of it and his

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platelets went back up, correct?
A. I mean, the dechallenge portion of that just refers to stopping the medication.
Q. And then you looked to see if it stops the side effect, correct?
A. Sure. Yeah.
So you take someone off the medication, and then you observe them. I think that's an okay definition of a dechallenge here.
Q. And that's pretty good evidence of a causal link, correct?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. I think the same caveats I applied to the previous case report I would apply here. But again, this is a case report, and this one in particular is -- is from quite some time ago, from, you know, almost 40 years ago.
And it's very difficult to know the complete clinical circumstances of -- of the patient in terms of what else might have been going on for co-associations if relevant or other lifestyle factors.

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Like, it's -- it's very difficult to know based on an N of one, one patient. You can't really use that to make inferences more broadly about causal links. So --

BY MR. VAUGHN:

Q. Did you -- sorry.

A. It's all right. Go ahead.

Q. Do you see here, even though this is a 40-year-old study, they are citing to other studies that have already been done where 26 to 71 percent of patients have a decrease in their platelet count when they're on thiazide diuretics, correct?

MS. ROSE: Object to the form.

THE WITNESS: I would have to review those studies. I mean, I'm not familiar, you know, with Kutti and Weinfield's study.

But if I just focused on what you're saying, they say that 26 percent of 71 patients receiving oral diuretics had platelet counts less than 100,000. They're actually not discussing trends there. They're just saying 26 percent of 71 had a platelet count of less than 100.

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The reason why I think it's so dangerous to extrapolate from, you know, from very limited case reports and even case series is why were those patients started on diuretics?

Were they started on diuretics because they had evolving liver disease and cirrhosis?

Fluid overload is a very common symptom of advanced -- you know, of decompensated cirrhosis, and we start patients on diuretics for that purpose. Or they may develop edema in the lower extremities, and we start patients on diuretics.

So unless you are controlling for factors like this, you can't say that, you know, the other comorbid factors are explaining why the platelet count is low. You can't attribute it to the hydrochlorothiazide without very detailed and careful study of potential confounding factors.

So I always hesitate to -- to extrapolate from case reports and case

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series. So the ones that you've shown me, these case reports, I don't find them compelling; and I would never extrapolate to say that they were the cause of Mr. Roberts' declining platelet count, especially in light of the very, very well-established scientific and medical basis for platelet counts declining in the setting of cirrhosis and portal hypertension, which we know is present in him.

So sometimes you can look at this almost as a weight -- weight of probabilities. You know, we try to determine what's most likely when we look at a patient.

I have a preponderance of -- of reasons to suggest that platelet count is declining in Mr. Roberts because of his cirrhosis and portal hypertension. That is further substantiated the deeper you go into the record. You know, the platelet count keeps going down as -- as he progresses toward decompensated cirrhosis in terms of a trend. It trends further

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downward.

So I have lots of data points in my mind that that support that balanced against these isolated case reports where this has not been systematically studied. I have no idea what the potential confounders are. This is a very brief case report. This is not even really a full page before they begin to site some references. It's extremely terse.

So -- so yeah. And so if I were to weigh the probabilities, you know, cirrhosis and portal hypertension is extremely likely. HCTZ, which we use all the time -- all the time in medicine -- I have so many patients who take HCTZ where we don't observe this. That is very, very low in terms of probability of explaining why his platelet count is declining in my view.

BY MR. VAUGHN:

Q. So when you came to your opinions in this case, you didn't consider the thiazide diuretic or the PPI as a cause of his thrombocytopenia, correct?

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MS. ROSE: Object to the form.
THE WITNESS: I looked at his medical list. I was aware that he was on the PPI. I was aware that he was exposed to hydrochlorothiazide.
In my clinical experience, you know, with these medications that I prescribe personally to many patients, that I manage patients who are frequently on these medications, these are not typical side effects that we observe in clinical practice.
Again, I'm not discounting the possibility that a very unusual case could occur where someone does have, you know, low platelets attributable to these things; but it's very, very unlikely and not something that we see in routine clinical practice.
BY MR. VAUGHN:
Q. I am going back to your expert report. I'm on page 8.
A. Okay. All right. Page 8.
Okay. I'm there.
Q. On this 4/19/2016 CT scan, you note

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that the radiologist says, "Although nonspecific, the findings above may be evidence of liver cirrhosis."
What does that mean, "nonspecific"?
A. So, you know, I'd be speaking on behalf of the radiologists. So I don't necessarily know what that particular radiologist may have meant by that.
But in my experience reading radiology reports and talking to radiologists, they usually mean this to be that there -- there might be some uncertainty in their view that there could be cirrhosis.
Q. And then you note 9/19/2016 was when Mr. Roberts was first exposed to NDMA-contaminated Valsartan, correct?
A. Yes.
Q. Okay. And then 10/17/2016 is the first time his doctors actually diagnosed his thrombocytopenia, correct?
A. Yeah. That's -- that's my first time I recall seeing a physician specifically mention the issue in -- in their clinical documentation.
Q. All right.

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MR. VAUGHN: Can we make that exhibit, I think, 13, Kathryn, the 10/27/2016.
MS. AVILA: Give me one second. I lost it.
MR. VAUGHN: You're fine. And if you need me to drop it to you, let me know.
MS. AVILA: Here it is. Exhibit 13.
(Whereupon, Exhibit 13, Medical Record, Bates labeled Restricted Confidential Information GRobertsJr-AMG-000040, was marked for identification.)
THE WITNESS: Okay. I think I have it.
BY MR. VAUGHN:
Q. What was that?
A. I have it. Sorry.
Q. Okay. All right.
So this is 10/27/2016, and this is Dr. Sanders is saying, "His platelets are low, and I'm not sure why," correct?
A. Yes. And I remember this. I think

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I quoted this, a lot of this section specifically because he specifically then says, "He is not on any medications that could be causing this."
And in looking back, this was not a problem during his last CBC.
Q. So this is a new prob- -- this is a new onset problem as of 10/27/2016, correct?
MS. ROSE: Objection.
THE WITNESS: Well, you know, as I -- in my view, it's not -- that's the first time that Dr. Sanders is specifically flagging this.
But as we've already stated, you know, he had a prior lab in November 2015 when he had an abnormally low platelet count in my view.
BY MR. VAUGHN:
Q. But his treating physicians didn't look at it as abnormally low, correct?
A. You know, I don't know. I can't -- I can't speak on behalf of the physician. This is the first time that his primary care doctor specifically mentions it. Whether or not he took note of it mentally previously and didn't

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document something, I can't speak to that.
Q. And just because the doctor's not any medications that could be causing it, that doesn't mean the doctor actually did research into PPIs of HCTZ to see if it could be cause, correct?
A. I mean, I can't really speak to what Dr. Sanders may or may not have done. What I can say is it's clear that he's thought about medications here as being a potential cause, and he's documented that specifically. So I would assume that he looked through the relevant medications that Mr. Roberts was on to make that determination.
Q. Because in clinical practice, that's what you should do, right?
You should look through all the medications and see if one of them were the cause?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. I think in clinical practice, again, you should -- you should think about the entire patient context and try to interpret a patient's labs and findings in the entire context.

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So that in some cases may -- may involve looking at the medications with a lot of scrutiny.
In other cases, to be quite frank, if a patient has a very obvious reason to have a finding, you may need to spend less time scrutinizing a very unlikely cause and put more of your emphasis on managing and evaluating and treating what's right in front of you.
So that -- that's an important clinical principle as well. You know, we -- as clinicians, we have to dedicate our time with our patients and our medical expertise, we have to put it to the area where it's going to be most beneficial.
Where it makes a lot of my sense, in my view, to scrutinize a medical record -- sorry, a medication list in great detail to try to find an explanation for a low platelet count is someone for whom you really have no other explanation.
If Mr. Roberts did not have, you know, chronic liver disease for decades and cirrhosis and portal hypertension and

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really no other identifiable condition that would be known to cause low platelets and then seemingly out of nowhere had a low platelet count without any other alternative expla- -- explanation, that's a scenario where you would very deeply scrutinize a medication list to try to understand what is going on.
But that's -- that's simply not the case for Mr. Roberts. He has very obvious explanations for why his platelet count is low in my view. And so -- you know, so I'm attending to the things that I think are most relevant in this case.
BY MR. VAUGHN:
Q. And so is that why you did not need to deeply scrutinize his medication list?
MS. ROSE: Object to the form.
THE WITNESS: Again, I'm not saying I didn't deeply scrutinize the medication list. As I stated previously, I reviewed his medications that he was on at that time. I reviewed the medications that he had been on at various points during his medical history.

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But in the context of -- of Mr. Roberts' comorbid medical conditions, imaging, other lab findings, FIB-4, I had a very clear interpretation and understanding for why the platelet count would be declining; and that was substantiated on his imaging that he had shortly after the low platelet count.
So in my mind, there really wasn't much uncertainty as to why his platelet count would behave in this way, trending downwards.
BY MR. VAUGHN:
Q. And as of 10/27/2016, Mr. Roberts had not been diagnosed with chronic liver disease, correct?
A. Sorry. As of 10/27...
Q. 2016, the date of this record, he had not yet been diagnosed with chronic liver disease, correct?
A. No. I disagree with that.
Chronic liver disease is inclusive of, you know, MASLD, NAFLD, MASH, NASH; and he had been known to have fat in the liver and abnormal transaminases for a long time.

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As -- as we've talked about previously, you know, since he was a teenager, he had abnormal transaminases.

You know, the definition of chronic liver disease is having transaminases, AST, and ALT that are abnormal for at least six months that are, you know, plausibly attributable to some chronic inflammatory process.

Mr. Roberts very clearly met those criteria for a long time prior to 2016, likely since he was a teenager.

Q. As of 10/27/2016, Mr. Roberts had not been diagnosed with cirrhosis, correct?

A. So as of 10/27/2016 -- so again, I'll not that, you know, his CT scan imaging the possibility of cirrhosis was raised on, you know, April 19th, 2016.

You know, I would agree that he -- it doesn't appear that he was given a formal diagnosis of cirrhosis by his treating physicians until a bit later in his medical history; though, you know, as you know, my view is that he had already had cirrhosis at this point.

Q. As of 10/27/2016, Mr. Roberts had

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not been diagnosed with portal -- portal hypertension, correct?

A. He had not been given a formal diagnosis of portal hypertension at that time point; though, again, in my review of his records, I believe portal hypertension was very, very clearly present as indicated, you know, really confirmed on his CT scan from April of 2016.

Q. And Mr. Sanders, his treating physician, can't figure out why his platelets are low to 10/27/2016, correct?

A. Yes. I would agree. That's -- that's his assessment. He said he's not sure why it is low.

Q. And as of 10/27/2016, his treating physician, Dr. Sanders, specifically says, "There is no appreciable splenomegaly, "correct?

A. Yes, yes. He does say that, and what I interpret that to mean is he, on physical exam, does not appreciate an enlarged spleen.

Q. Even though he just had imaging done months prior?

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A. Yeah. So the -- the physical exam for detecting an enlarged spleen is extremely unreliable. It's a very difficult technique that requires, honestly, a lot of experience and -- and dedicated experience to identify an enlarged spleen reliably on exam.

Cross-sectional imaging is vastly superior to the physical exam for identifying an enlarged spleen because you can see the spleen directly and measure the spleen directly.

So it's -- there's really no question on a CT scan if it's -- if it's present or not, you know, assuming a qualified radiologist reviews it.

Q. What is your basis that he is saying this based off of a physical exam and not the imaging, or are you speculating?

MS. ROSE: Object to the form.

THE WITNESS: So that's -- that's a good point. I mean, he may have looked -- I can't rule out the possibility that he may have looked at the CT scan. I suspect he -- if he did review the imaging, the CT scan, he probably reviewed the

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radiology report, where that particular radiologist did not comment on the spleen being enlarged.

So yes. I mean, I -- I -- I'd have to see again his physical exam from that visit to see if he -- maybe he mentions it. I'm not sure. I'm trying to see.

Yeah. I -- I guess we just have this one page. I think it would have been on a page above this one, perhaps, where in his documentation of the physical exam, if he specifically says "no splenomegaly, no enlarged spleen on exam," that would make it very clear that he's basing this on his physical exam.

BY MR. VAUGHN:

Q. If there was an enlarged spleen on imaging, is the radiologist supposed to note that?

MS. ROSE: Object to form.

THE WITNESS: Yeah. I -- I -- I had mentioned before that there is quite a range in quality and expertise of radiologists, as there are in any field. You know, I mean, I'm sure it's the same

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with lawyers.
So you have some radiologists that are extremely good at what they do and some who are -- maybe they're more generalists where they read a wide variety of different types of imaging but they don't specialize in body radiology.
And then sometimes they -- they don't -- or they're not really attending to a specific area of the body, or they're really attending to an area in response to the reason for the imaging study.
So yes. I think best practice would be to do a detailed review of all the organ systems that you see on, you know, an abdominal CT, for instance, and then to comment accurately on what you think is present or absent.
But it is in very common, you know, in my practice, where, you know, a radiology report may not note something that is, in fact, there that is later corrected or identified in retrospect by a more qualified radiologist or after a discussion with another physician who may

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have reviewed it who then discusses it with the radiologist and they would amend the report and say, you know, after re-review there is, in fact, splenomegaly present. That happens all the time.
BY MR. VAUGHN:
Q. Do you have any opinion if it was a minor enlargement of the spleen or if there was a significant enlargement of his spleen?
A. So it's usually kind of regarded to be a binary is it enlarged or not in general. And I know we talked about the spleen in -- in some detail before.
And actually, if it's okay with you, Counselor Vaughn, while -- while we're on that subject, I had wanted to correct something I said previously about the splenomegaly on this CT scan very briefly. I'll get back to your question.
I think I previously stated that both expert radiologists from the plaintiff and the defense side had stated that there was splenomegaly on the CT scan. I looked at my expert report again, you know, during one of the breaks. I was scrolling through that

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section of my report. I think it was only Dr. Mele who commented on the splenomegaly. Dr. Chernyak didn't comment on the spleen at all. They're both in agreement that there's cirrhosis, but only Dr. Mele specifically commented on the spleen size, and he measured it at 16 centimeters.
I think I mentioned previously that, you know, above 12 centimeters is regarded to be an abnormally large spleen. So that's -- it's not really close to that threshold. I mean, a 16-centimeter spleen is -- it's -- it's clearly enlarged. It's very clearly enlarged. That's all I can say. It's very clearly enlarged.
So I apologize for the -- for that clarification.
Q. You're fine. All right.
Going back to your expert report, which is Exhibit 1 --
A. I apologize. Give me just a moment. I -- I accidentally closed the link.
Okay. I think I've got it.
Q. Okay. I'm on page 9.
A. Okay.

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Q. And here on 7/17/2018, his AST spikes to 440 and ALT to 429.
What is the significance of that, if any?
A. Yeah. So my -- my opinion of what happened here is I'll -- I'll just draw a contrast because it's very different than Dr. Siddiqui's impression of what the significance of these labs are.
I am of the same mind as Dr. Hooks, who is the gastroenterologist that, you know, was -- was seeing Mr. Roberts around this time.
When you see the AST and the ALT spike like this very acutely, especially with a bilirubin elevation, which you also see there was four. That's also abnormally elevated, and it was previously normal for -- the bilirubin was previously normal for Mr. Roberts. That is a very strong indicator of a gallstone that may be impacted in the common bile duct.
That is what Dr. Hooks was also worried about. Basically, normal -- normally bile will be produced in the liver. It will flow through the bile duct, down into the common bile duct, and out into the intestines.

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A gallstone can migrate into the common bile duct and cause a blockage. And so the bile has nowhere to go. It can't flow out into the intestines like it would normally. So it backs up into the liver and causes acute abrupt injury to the liver cells, the hepatocytes. And they spill out a lot of AST and ALT.

And the bilirubin also comes up because it's backing up, essentially, into the blood. So you -- that constellation of findings is very, very, very suggestive of a stone that has become obstructed in the -- it's obstructed in the common bile duct.

And that fits his clinical presentation too because he -- Mr. Roberts had gone to the emergency department with abdominal pain radiating to the back, which is a classic description of, you know, gallbladder or bile duct-related pain. Based on the way the nerves work in the abdomen, they're not very specific in the way that they route pain signals. So it's very common for patients to experience abdominal pain and back pain when this issue is happening.

So to me, this all fits very

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cleanly as the likely explanation. And Dr. Hooks was so concerned about this, that he -- I believe he pursued an endoscopic ultrasound to look for a gallstone.

Yeah. So I think I've noted that there a couple lines lower on the page. On 7/19 he performed an endoscopic ultrasound and an esophagogastroduodenoscopy. You know, he did this to look at the bile duct with an ultrasound from the inside to look for a stone. He did not find a stone. So that's when he says there's no evidence of a choledocholithiasis.

What that typically means is that the stone that was there that was causing the obstruction has passed, and that happens very commonly. These might be transient obstructions. They cause a big problem. They cause a lot of pain. People go to the emergency department because the pain is so bad. You see these constellation of labs. And by the time you do the ultrasound, the stone may have spontaneously passed.

And what -- what additionally supports to that is the fact that his labs very

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quickly return to their previous baseline. So his labs on 7/25, they come back down to an AST of 66, ALT of 79, total bilirubin of 1.1, which is in the range of what his previous baseline prior to this issue was.

So I think that he had a stone that was transiently obstructing the common bile duct causing his symptoms in these labs that spontaneously passed. That's the -- excuse me -- that's the assessment that Dr. Hooks has as well.

And I apologize for going on about this at such length, but the last thing I'll say is I -- I drew a contrast to -- to what the plaintiff expert witness, Dr. Siddiqui, had stated here. I mean, she -- she was basically positing in her deposition that these labs in July of 2018 where the AST and the ALT spiked would -- was -- was related to aggressive hepatocellular carcinoma, which I think is an important, you know, landmark to -- an important flag to plant here because she is really imputing that he would have had hepatocellular carcinoma on the basis of his NDMA exposure in a very short time interval.

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I think we had -- we had said that, you know. So this has been a less -- less than a year of exposure to NDMA-contaminated Valsartan, and she was attributing these labs to hepatocellular carcinoma.

Q. At this point it would have been approximately two years, correct, of exposure?

A. Oh, I'm sorry. Yes. I apologize. I -- I misspoke.

It's -- yes. This would have been -- yes. You're right. I apologize. It would have been about two years of exposure.

Q. And you said his labs returned -- dropped back down.

Which labs are you referencing?

A. So a little bit below the highlight that you have there, so 7/25/18, the labs were AST 66, ALT 77, total bilirubin 1.1.

Q. Up here on 7/18/2018, is this the first time he was actually diagnosed with splenomegaly by one of his treating physicians?

MS. ROSE: Object to the form.

THE WITNESS: This is the first time in the record where splenomegaly, I think, was specifically referenced, I

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think, in a clinical note. I think that is the case.
BY MR. VAUGHN:
Q. And even here in 7/18/2018, they're still just saying possible changes of cirrhosis of the liver. Not that he had -- he's still not being diagnosed with cirrhosis as of 7/18/2018, correct?
A. So I think this is -- and we could look at Dr. Hooks's clinical note. This is -- I don't think this is from a direct imaging report. This is -- I think this was Dr. Hooks paraphrasing the conversation he had had with Mr. Roberts.
You know, so -- so what I wrote there was, you know, he, Mr. Roberts, was told that, quote, "he had splenomegaly and possibly changes of cirrhosis of the liver." So I'm assuming that is what maybe Mr. Roberts had communicated to Mr. Hooks -- to Dr. Hooks, who then wrote that down in his note. So I think that's where the context in which that -- that quote appears.
Q. Okay. And this was 7/18/2018 that comes from?

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A. Yes.
Q. And that same day they did a CT where they noted an enlarged spleen of 17 centimeters and likely cirrhosis, correct?
A. Yes.
Q. And so he still has not actually been diagnosed with cirrhosis as of 7/17/2018, correct?
MS. ROSE: Object to the form.
THE WITNESS: Yes. I mean, it really depends on what you mean by "diagnosed with cirrhosis."
You know, whether he was definitively told by one of his providers this is cirrhosis, you know, it doesn't appear that that was the case based on his records.
But like I said, it doesn't change the fact that cirrhosis is present. I mean, cirrhosis is very clearly present at this time and prior.
But, you know, I would agree that I don't -- I don't get he the sense that Mr. Roberts was definitively told, you know, on 7/18/2018 that he definitely had

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cirrhosis.
BY MR. VAUGHN:
Q. Do you think it's clear that he had cirrhosis in 2018 than it was in 2016?
A. I think it is as clear then as it was in 2016, yeah. I think in April of 2016, there are multiple features on the imaging that, you know, are really, you know, in the -- in this clinical context of an elevated FIB-4, a declining platelet count, plus multiple imaging features of cirrhosis and portal hypertension, it's all entirely consistent with the diagnosis of cirrhosis.
If he was my patient at that time, I would have very clearly told him that he had cirrhosis, and I would have enrolled him in a cancer screening protocol for hepatocellular carcinoma as he should have been.
Q. Is it your opinion that Mr. Roberts' cirrhosis did not progress from 2016 to 2018?
MS. ROSE: Object to the form.
THE WITNESS: I -- I wouldn't -- it depends on what you mean by "progress." I mean, he still had a compensated cirrhosis

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physiology at this point. He doesn't have ascites. He doesn't have hepatic encephalopathy.
Did he likely accumulate some additional scar in the liver over -- over the kind of ensuing two years? He probably did because he still had MASLD and MASH. He still had elevated AST and ALT, indicating ongoing liver injury. So he probably did have, you know, additional scarring, but, you know, the -- the morphologic features of cirrhosis are very evident equally on both imaging studies. They look very similar from a cirrhosis standpoint.
BY MR. VAUGHN:
Q. And you looked at both imaging studies, correct?
A. Yes.
Q. And the imaging in 2018 did not look like the cirrhosis was more severe than in 2016 to you?
A. You can't really make a determination, quote/unquote, of how, you know, "severe" the cirrhosis is. You can

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determine -- you can infer how bad the portal hypertension may become. But it's -- it's oftentimes a little bit more binary from a cirrhosis standpoint on -- on imaging.

So, you know, his -- there is evidence that his portal hypertension is likely worse in 2018, and the evidence there is that his spleen size is probably a little larger than it was in 2016 when Dr. Mele measured it at 16 centimeters. So in 2018 it was measured at 17.3 centimeters. So that suggests the portal hypertension is likely a little bit worse. But the cirrhosis a-- as s a binary feature, the cirrhosis is present on both imaging studies.

Q. So does the an- -- excuse me.

Does your answer change any of the fibrosis?

Was Mr. Roberts' fibrosis any worse in the imaging in 2018 versus 2016?

A. So, you know, fibrosis, like I said, you know, the terminal staging of fibrosis is cirrhosis. F4 by the METAVIR staging is -- is cirrhosis. There's no fibrosis staging that goes beyond that.

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So if cirrhosis is present in 2014, by definition he has F4 fibrosis. There can be accumulating fibrosis beyond that; but from a diagnostic standpoint of cirrhosis, there's no additional stage.

So -- so yeah. There's nowhere else in the scale to place him. Like, he has cirrhosis in both settings. And then beyond that, the things you're looking for are evolution of worsening portal hypertension.

So yeah. So it doesn't really make sense to me, I guess, per se, to say that the, quote/unquote, "the cirrhosis appearance is more severe in one imaging than the other." It's more features of the portal hypertension that become more salient once the cirrhosis is already diagnosed.

Q. And what is the evidence of portal hypertension?

A. So there are multiple lines of portal hypertension. Maybe if I just very briefly explain what it is it'll make it pretty clear hopefully what I'm referring to on the imaging.

But basically, there's -- I said

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previously there's a very large vein that goes into the liver called the portal vein, and that drains -- that blood supply kind of drains the intestines and a lot of the gut. So many different veins feed into the portal vein and then go into the liver.

In the liver the portal vein, then, branches out into many, you know, microscopic small branches of the portal vein.

What happens in cirrhosis is the scarring happens very diffusely, you know, throughout the liver, and the scarring can basically squeeze on those microscopic portal veins. It's almost like a plumbing problem where you can image there's a pipe going through the liver. The scar in the liver is sort of squeezing around the pipe. So you get a pressure backup upstream, you know, of the pipe.

So you look for specific signs of enlargement of particular veins that normally would not be abnormally enlarged, and you -- and the other thing is the spleen is directly connected by a branch of the portal vein to the liver.

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So the spleen one of the organs that is very directly impacted by this problem. When there's a lot of scar, there's a squeezing of the pipe, the pressure backs up into the spleen, among other areas. The spleen gets congested because of that pressure and begins to enlarge. So that's why the splenomegaly is very relevant.

Another very important feature is something called an umbilical vein. This is a feature that both expert radiologists from plaintiff and -- and the defense side both com- -- acknowledge and comment on is that Mr. Roberts has something called a recanalized umbilical vein. What that means is he has an umbilical vein that is open. You can see that it has blood flowing through it.

Normally that does not happen in adults. If the umbilical vein is as -- as the name would suggest, it's -- it's seen in infants when you're first -- when someone is born, they're attached to the mother through the umbilical vein and, you know, the umbilical, you know, artery as well.

And so but that as -- as you grow

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into -- into, you know, even in pediatrics, it closes up relatively quickly from my recollection. But certainly in an adult that should not be open. It's entirely closed. You only see that open up when there is portal hypertension. It's pathognomonic for portal hypertension.

Pathognomonic just means that if you see it, it is -- it is an indication that there's portal hypertension present. You will not see it if there's no -- if there's no portal hypertension.

So Mr. Roberts has all of these features in 2016. He has all these features in 2018. And the spleen being enlarged, it's -- it's also sort of a filter of sorts where it traps platelets. So the larger the spleen gets, the lower the platelet count is expected to get as well, which is why if things tend to trend downward over time as the portal hypertension worsens.

So I'm relying on those things. I'm relying on the platelet count, the spleen size, the recanalized umbilical vein. Those are the primary pieces of evidence on these

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scans that there is very clearly portal hypertension present.

Q. And the spleen being enlarged, I think you were just mentioning, that's like congestion. So, like, fluid is backing up, and there's congestion that makes the spleen enlarged.

Is that the correct way to think of it?

A. Yeah. I think, you know, that's -- that's a -- yeah. That's a -- that's a very simplistic way is to explain it is, yes, it's under high pressure. The spleen experiences that pressure and will start to enlarge.

Q. And did you continue reviewing Mr. Roberts' labs after he was diagnosed with liver cancer?

A. Yes, I did. I think I -- you know, I highlighted ones along the way that I thought were relevant to his clinical course. You know, certainly, for instance, you know, I highlight some of his tumor-related markers, you know, where I thought was relevant.

His alpha-fetoprotein, I think I highlight that on August 22nd, 2018. And, you

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know, I think wherever I was able to calculate a FIB-4, I think I did so.

So, you know, in December of 2018, he had the requisite labs sent to calculate a FIB-4; but oftentimes, he might have piecemeal, like, he might have an AST and an ALT sent off, but not the platelet count, so I wasn't able to compute a FIB-4.

So, you know, I'm not giving an exhaustive summary of all of his labs, but I'm trying to highlight the ones that were most relevant and pertinent to my opinion.

MS. ROSE: Mr. Vaughn, just for the record, we've been going for over an hour. So I just wanted -- wanted to let you know whenever you reach a good stopping point.

MR. VAUGHN: I was just about to say, if you would like to take a break, I'm at a good stopping point.

MS. ROSE: Doctor, would you like to take a break?

THE WITNESS: Sure.

THE VIDEOGRAPHER: Off the record at 3:51.

(Whereupon, a break was taken.)

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THE VIDEOGRAPHER: We are back on the record at 4:03.

MR. VAUGHN: All right. Kathryn, if we could drop in the 6/19/2017 record, I believe this will be Exhibit 14.

(Whereupon, Exhibit 14, Medical records, Bates labeled Restricted Confidential Information GRobertsJr-AMG-000032 through Restricted Confidential Information GRobertsJr-AMG-000036, was marked for identification.)

MS. AVILA: Yes. It's in there now.

THE WITNESS: Okay. I have it up.

BY MR. VAUGHN:

Q. This is the 6/19/2017, correct, Doctor?

A. Yes.

Q. And he was having an office visit for the thrombocytopenia?

A. Yes, yes. Well, I guess there's multiple -- multiple diagnosis codes that are there. So among other ones, there's thrombocytopenia there.

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Q. Thank you for that clarification.
A. Okay.
Q. And his doctor notes that he has a history of thrombocytopenia based on his last visit of October 2016, correct?
A. Yes.
Q. Okay. And October 2016, that's after he started NDMA-contaminated Valsartan, correct?
A. Yes.
Q. Okay. And if we go to the actual labs he's referencing for thrombocytopenia, it shows a platelet count of 127, correct?
A. I'm scrolling through.
Yes. I see that. 127, yes.
Q. And at reference range here, that bottom end of normal, is 130, correct?
A. Yes. That's the reference range reported by this lab, again, with the same caveats that I provided, you know, previously about my -- my interpretation about the platelet count.
Q. And the lab is noting that the 127 this time is abnormal, correct?
A. Yes.

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Q. And is that the first time that we've seen the lab actually say that his throm- -- that his platelet count was abnormal?
A. I think that's the case. Yeah. If I recall -- I'm trying to recall the reference. Yeah. I think in the November 2015 one we looked at together when it was 137 -- I can't even recall what the reference range was for that lab.
Q. Okay.
A. Was that one 1- -- 140?
Q. That one was 130. The one where his platelets were 174, the lower limit of normal was 140.
A. Gotcha. Yes. Then I would -- I would agree with you. This is the first time that the lab has flagged this as abnormal.
Q. And the doctor, his treating -- scratch that.
Mr. Roberts' treating physician is not considering him thrombocytopenic until his lab is actually abnormal, correct?
A. Yeah, that seems to be the case. And perhaps that's why, you know, this is the time when, you know, thrombocytopenia is

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specifically noted in his -- his office note.
MR. VAUGHN: And then, Kathryn, can you drop the 2000 -- the 12/13/2018. And what exhibit is this going to be?
I'm off on my numbers. I'm sorry.
MS. AVILA: Yes. This will be Exhibit 15.
MR. VAUGHN: It is 15. Thank you.
(Whereupon, Exhibit 15, Medical records, Bates labeled Restricted Confidential Information GRobertsJr-SouCC-000235 through Restricted Confidential Information GRobertsJr-SouCC-000238, was marked for identification.)
BY MR. VAUGHN:
Q. All right. Doctor, this will be the 12/3/2018 visit for Mr. Roberts, correct?
A. Yes, 12/3/2018, yes.
Q. And at this point, he has been diagnosed with Stage 3A hepatocellular carcinoma, correct?
A. Yes.
Q. What does Stage 3A hepatocellular carcinoma indicate?

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A. This indicates that he does not have early stage HCC. This is an HCC that is generally beyond transplant criteria.
I'll say that, you know, in our practice we -- we typically use a different staging schema these days. It's possible that -- you know, I think in 2018, perhaps, a different nomenclature was commonly used.
These days we used something called the BCLC staging, the Barcelona Clinic Liver Cancer criteria staging; but I see it's not framed in that fashion here. This is something called the NCCN staging.
So I can't recall, like, the specific delineations of thresholds that move someone from Stage 3A, Stage 3B. But generally speaking, this is not an early stage hepatocellular carcinoma, and it's not one that can be, you know, generally cured with liver transplantation, unfortunately.
Q. What was the other staging that you talked about that can be used?
A. It's called the BCLC staging. It's in my expert report. Just checking to see if I -- yeah. I reference this on page 16 of my

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expert report if it's of interest, but it's called the Barcelona Liver -- sorry, Barcelona Clinic Liver Cancer classification. That is really the state-of-the-art classification schema that's used for -- for staging HCC in the modern era, like the current era of practice. It also helps inform management and treatment of HCCs of different stages.

Q. And when did BCLC become will the common staging to use?

A. Let me tell you. So the most recent iteration of the BCLC, the one that we use currently, it's relatively recent. So this was published in the Journal of Hepatology in 2022. The first author is, I think it's Marta Reig, R-E-I-G. It's a 2022 publication with the current -- the current BCLC staging criteria, which I understand postdates this note.

Q. And does Stage 3A correspond to any BCLC?

A. Yeah. I -- I mean, I'd have to look specifically to confirm, but I'm fairly certain that this would correspond to a BCLC Stage B hepatocellular carcinoma.

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Q. And do you see here where the doctor says, "The CBC results were reviewed, and counts were noted to be within normal limits"?

A. Yes, I see that.

Q. And that -- that would indicate that this physician, his treating physician, believes that his platelets are within normal limits on 12/3/2018, correct?

A. Yeah. That's what this statement says. I would need to see what the CBC actually is. I don't know if they have the platelet count there reported or other values.

Q. Right here, 142.

So his treating physician is considering a 142 platelet count from this lab to be normal, correct?

A. That's -- that appears to be their interpretation. It may be the case that this lab similarly has a lower end of normal, maybe 140 or something where it doesn't flag it as abnormal. But again, to hepatologists like myself, that is abnormal. It is still thrombocytopenia.

Q. And his platelets have now

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increased a little bit from the last platelet we had at the time of his cancer diagnosis, correct?

A. Yes. It is slightly higher, I think, than the previous one we looked at together.

Q. Do you have any explanation for why it would have increased some at this point?

A. Sure. Sorry. What was the previous -- I'm trying to remember the degree of change. Let's see if I can find that. All right.

So it was one -- in 2015 it was that. So ins 2016 it was 127. I think that's the last one we reviewed.

Is that your recollection as well?

Sorry. I don't mean to interrogate you.

Q. No, no. You're fine. We -- we did review that one, yes.

A. Okay. Regardless, I mean, yes. It's changing on the order of maybe 20 points or so or maybe less.

Yeah. So I think I mentioned before that, you know, platelet counts, they

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can fluctuate very commonly based on a lot of different factors.

So, you know, for instance, time of day is one factor. I mean, if you check someone's platelet count in the afternoon, it tends to be a little bit higher than in the morning. Things can vary based on your hydration status. So if you're more dehydrated, your platelet count will be usually a little bit higher because of something called hemoconcentration.

Or if you have -- if you're infected, that's a stress state that can drive the platelet count a little bit higher. There are certain medications, like, you know, Prednisone that can cause something called demargination that drives the platelet count higher. There's lots and lots of things that -- that can cause platelet counts to fluctuate from one lab test to another, which is why, you know, again, I keep emphasizing the importance of looking at trends in platelet counts and not really relying on one particular instance.

You know, to me, this is -- this is

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a fluctuation that, to me, is still abnormal. It's still low. It's not dramatically different, I wouldn't say, from his prior platelet count that we reviewed together; but, you know, at this time he's, you know, he's certainly sicker. He probably has, you know, some degree of stress response that's occurring in the setting of his somewhat advanced cancer at this stage. So it's not unusual to see the platelet count come up a little bit in that setting.

Q. So would you consider the 20-point variation to kind of just be in the normal variation that you would see from test to test.

A. Yeah --

MS. ROSE: Object to the form.

THE WITNESS: I'm sorry.

Yeah. It doesn't strike me as unusual. It doesn't really change any of my opinions about why the platelet count is -- is -- continues to be low in my view.

So yeah. This is -- this is a fluctuation that doesn't really have much clinical significance in my opinion.

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BY MR. VAUGHN:

Q. Would it mean that his portal hypertension is doing better at this point?

A. No, I wouldn't say that. In fact -- sorry. This 20- -- this is December 2019, right?

Q. Uh-huh.

A. I apologize. I was looking for one thing in my note.

So it's actually -- it's very clear that his portal hypertension is worse at this time because at this point in his history, he has developed decompensated cirrhosis. He has manifested ascites as a clinical symptom of his cirrhosis, which he --

MS. ROSE: Can I -- I'm -- I'm sorry. I feel like there's some confusion because I feel like you both just said this was a 2019 record.

Are we still looking at -- I'm sorry. I don't mean to interrupt.

But are we still looking at --

MR. VAUGHN: I haven't changed the exhibit.

MS. ROSE: Oh, so it's a 2018

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record, correct?

THE WITNESS: I apologize.

MS. ROSE: I'm sorry. I just -- you said it's a 2019, and then --

BY MR. VAUGHN:

Q. I think she was probably interrupting you because you said that he had ascites at this time.

Did he have ascites at this time in December of 2018?

A. No, no. He did not. I apologize. I got mixed up with the year. I know in 2019 he had ascites, yeah. Let -- let me -- allow me to correct that. I apologize.

Yeah. At this time he did not have ascites. This is -- this is 2018.

So yeah. I mean, it's hard to mean to determination of, you know, is the portal hypertension better or worse. But I -- he doesn't really have any reasons for it to be better. So it's likely that his portal hypertension is a little bit worse. But he is in a higher state of kind of basal stress in the setting of -- of having this cancer.

So it's not unusual to see platelet

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fluctuations, you know, in his this range. And I think that even shortly after this one -- this is from 12/3 -- you know, as -- as an illustration he has labs checked on again 12/18 of 2018, and his platelet count is 126.

So this does fluctuate, and, you know, you're trying to get a sense of the trends and the general range where it is currently. So I don't read too much into this isolated platelet count bumping a little bit relative to the previous value.

Q. But you do read into it bumping down a little bit when it does?

A. No, I don't. I don't. I -- I -- like I said, I'm just -- I highlight that just to show you it can fluctuate up and down. If the trend over time is -- it is gradually dropping lower and lower. You know, I think 126 might have been, for instance, like, a new low value for him.

But in my determination, I've already -- it's already established that he has cirrhosis and portal hypertension. So, you know, to me, perseverating on the platelet count is not as relative as managing the

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clinical symptoms and the cancer at this stage.
It's not really disputed that he has cirrhosis and portal hypertension by anybody at this point. And so the platelet count is, you know, it's not really the most important thing in his record in my view.
Q. Are the platelet counts important prior to this diagnosis?
A. Yeah. I think they're -- they were very important. I mean, they're important, of course. I think the area in his record where I think they're probably most important are in facilitating and understanding of when he likely had cirrhosis and what should have helped prompt him to have been evaluated by, ideally, a hepatologist to try to establish the diagnosis. And then trying to establish, you know, and understand what degree of portal hypertension he may have.
At this point it's very clear that he has evidence of portal hypertension, the splenomegaly, the recanalized umbilical vein.
So, you know, I have an understanding already of why his platelet count is in this range. So sure, the platelet count

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may continue to trend down gradually; but if it were to go up a little bit, I wouldn't suddenly say that, okay, his portal hypertension is gone because that's not the way that cirrhosis pathophysiology works.
Q. Did you look in his pharmacy records to see if any medications were dis- -- scratch that.
Did you review Mr. Roberts' pharmacy records to see if any medications were discontinued right before his platelet count increased?
MS. ROSE: Object to the form.
THE WITNESS: As before, I reviewed his -- his, you know, medications throughout his course. But, you know, I can't recall specifically if there was a medication that was stopped, you know, prior to this one. But I'm happy to review that with you.
BY MR. VAUGHN:
Q. Okay. Let's go back to Exhibit 11, which was his pharmacy records. And let's see here.
Would you agree with me that his,

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Mr. Roberts', last dose of NDMA-contaminated Valsartan with HCTZ was filled on 6/13/2018?
A. Yes. That -- yeah. That appears to be the case from this document.
Q. And it was a 90-day fill, correct?
A. Yes.
Q. And 90 days after 6/13/2018 would put us somewhere around the middle of September 2018?
A. Yes, that sounds about right.
Q. And his next CBC his platelets went up, correct?
A. Yes, his next CBC, the platelets are up a little bit.
Q. And we discussed earlier how HCTZ can impact platelets, correct?
MS. ROSE: Object to the form.
THE WITNESS: You showed me a case report from 40 years ago that, you know, that basically made, you know, the observation that somebody who was started on HCTZ was observed to have a platelet count that went down. And then they stopped it, and it went back up a little bit.

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And, you know, I apologize. Just to add one more parenthetical, yeah, as I mentioned a moment ago, the subsequent platelet count that was checked very shortly afterwards was, once again, 126.
So, you know, if the implication that you might be suggesting is that stopping the HCTZ is why the platelet count went up by, you know, 15 or 16 points, that would not be a viable explanation given that, you know, only, you know, two weeks later the platelet count is back to 126 while he's still off the medication.
So I don't -- I don't view that to be, you know, compelling.
BY MR. VAUGHN:
Q. Did you do any research in coming to your expert opinions if NDMA could cause the spleen to enlarge?
A. That's a good question.
I don't recall coming across studies that specifically were investigating NDMA exposure and spleen size.
MR. VAUGHN: Kathryn, can you drop

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in 2008 WHO for Exhibit 16.
MS. AVILA: Yes. It's in there. It's Exhibit 16.
(Whereupon, Exhibit 16, Document entitled "N-Nitrosodimethylamine in Drinking-water, Background Document for Development of WHO Guidelines for Drinking-water Quality", was marked for identification.)
BY MR. VAUGHN:
Q. All right. Doctor, this is from the WHO.
Do you know what the WHO is?
A. Yes. It's the World Health Organization.
Q. Okay. And they put this out in 2008 called N-Nitrosodimethylamine in Drinking-water.
A. Okay.
Q. Have you seen this document before?
A. I'm not sure if I saw this specific one. I may have. I did -- I did review some -- I certainly reviewed a number, you know, several different NDMA-related publications from WHO. I can't immediately

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recall if I saw this specific one.
Q. If we go to page 8, I believe, it's page 16 of the PDF.
A. Okay. 16?
Q. Yeah. Do you see here where the World Health Organization says, "In addition to effects in the liver, congestion, excessive blood, fluid content in a variety of organs, i.e. kidneys, lung, spleen, and myocardium, has been reported following examination of rats receiving NDMA."
Were you aware of that?
A. Yeah. I don't recall coming across this, you know, specifically. But just kind of reading the full context here, you know, this looks like it's from an animal study of rats who were receiving what seems like an exceptionally high dose of NDMA of, you know, 3.8 milligrams per kilogram per day, which is an extraordinarily high dose relative to exposures, you know, that have been observed in human studies and certainly orders of magnitude higher than what Mr. Roberts was exposed to.
Q. And so are you disagreeing that NDMA can cause the spleen to enlarge?

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MS. ROSE: Object to the form.
THE WITNESS: Yeah. So -- so the statement here, it's actually not commenting on enlargement of organs. It's talking about congestion. That doesn't, you know, necessarily mean that there's going to be enlargement of an organ.
But, you know, I acknowledge, you know, I'd have to review the study, the particles to understand the methodology. But I take them -- I take them at their word in this report that with high dose NDMA exposure, if they see evidence of increased blood flow in different organs, I don't have any intrinsic, you know, reason to doubt that in -- in this study in rodents.
BY MR. VAUGHN:
Q. And you say that you would need to review the study.
You didn't review this study prior to coming to your expert opinions, correct?
A. I don't recall the specific study. It's very possible that I did come across it, but I'd have to see that study -- I'd have to

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look through it again to jog my memory.
There were many different studies, obviously, that I reviewed. I cited a large number of studies. It's hard to immediately recall each one of them in detail.
Q. And just a few minutes ago, you testified that splenomegaly was caused by congestion or excessive fluid, correct?
A. Yes. I did -- I explained that congestion in the setting of elevated portal pressures can lead to growth of the spleen.
So I -- I use the term "congestion" to facilitate an understanding of what high pressures can do, but that's not meant to imply that congestion in all cases in the absence of elevated -- elevated pressures may translate to enlargement of the spleen. I was describing that specifically in the context of portal hypertension and cirrhosis.
Q. And these are rats that they gave NDMA to. They only gave it to them for 1 to 12 weeks, right?
A. Yes. They gave it to rats for 1 to 12 weeks.
Q. And Mr. Roberts was taking NDMA for

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approximately two years, correct?
MS. ROSE: Object to the form.
THE WITNESS: Yes, he was taking NDMA for approximately two years. But the two, I think, important points I -- I would just highlight very briefly are, again, that the magnitude dose exposure is -- is very, very different here; and the second important point that I think actually has not been touched upon in any of the depositions I've reviewed from toxicologists, et cetera, is that the lifespan of a rat is very different than a lifespan of a human.
You know, rodent lifespans are on the order of two years. So one to -- so, you know, three weeks of exposure -- sorry. Three months of exposure 12 weeks to, you know, in a rodent study, that's equivalent to potentially more than a decade of exposure in a human. So you can't translate time for rodents one to one to humans.
Yeah. At the top of our deposition, I highlighted that the FDA

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understands this; and that's why they frame their dose threshold exposure for NDMA in terms of a lifetime of human exposure over 70 years.
So it's -- it's a major fallacy to try to translate a time course of exposure in a rat to being equivalent to a time course of exposure in a human. Three to six months of exposure in a rat is decades of exposure time in a human. So I need to make that point really, really clear.
BY MR. VAUGHN:
Q. Are you a toxicologist?
A. No. I've stated multiple times I'm not a toxicologist, but I am a clinician. I'm a clinician scientist. You know, I'm acquainted with, you know, reviewing animal literature, you know, to an extent in the course of my, you know, my practice as a clinician and as a clinician scientist. And I understand these principles.
You know, we get educated about these things in medical school, you know, when we learn about animal literature and how -- what the context in which animal literature is

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used -- you know, what the role is in the scientific process to understand the relevance of a drug or a new exposure and how that may or may not translate to humans.
So I'm relying on my perspective with that background, but -- but that's, you know, that's my understanding of why you cannot simply take a multi-week exposure in -- in a rat and say that the same multi-week exposure should have the impact in a human.
Q. And you didn't give that expert opinion in your report, did you?
A. I did not give that expert opinion in my report. The reason I bring it up is because I reviewed the deposition of Dr. Siddiqui this week where she offered that opinion. So I'm trying to be responsive to what the plaintiff expert witness stated in her report.
I -- I recall specifically reading her deposition that, you know, she is saying that, you know, in -- in rodents over the course of weeks' long exposure -- and actually, I think that -- my recollection was it's really more in the order of, like, maybe three to six

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months on the earlier side on the animal literature, you might see an association between NDMA and liver cancer.
So I'm responding to, you know, the plaintiff expert witness's statement, which, you know, she didn't offer that opinion, to my recollection, in her initial report. This came out in her deposition.
So I'm specifically offering that opinion in response to hers.
Q. And did you produce any literature to support that opinion before this deposition?
A. No, I did not. I mean, I read her deposition, I think, yesterday; and -- but I'm not relying on literature that hasn't already, you know, been disclosed. I'm happy to -- to offer that. If necessary, I'm happy to review this and supply literature if it's helpful.
But I'm relying actually on, you know, the FDA-related documents to -- as an illustration of this because the FDA very clearly states in their industry guidance regarding NDMA and the threshold levels that these are the dose exposure levels for a human lifespan over 70 years, where they would expect

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to see one additional cancer per 100,000 individuals with that exposure. And that's translated from -- from animal studies.

So the reason why they extend it over 70 years is because the lifespan of a rodent is about roughly two years, and they basically do calculations, you know, from the dose exposures in animal studies. They set a conservative margin, and they translate that to a human lifespan.

So that's why the -- the FDA doesn't say this dose exposure for a period of weeks. It's a period of decades, decades.

So I'm trying to contextualize these documents that I think all of us have reviewed related to the FDA.

Q. What was the highest level of NDMA that the FDA was aware of in Valsartan pills?

MS. ROSE: Object to the form.

THE WITNESS: I'd have to review -- you know, we can look at whether the toxicology reports -- I think Dr. Sawyer gave the ranges. You know, I can't, you know, give you off the top of my head, like, what the exact number was for the

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highest.

But, you know, it's in the range of, if I'm just trying to recall -- you know, 20 micrograms was one of the higher end estimates for Valsartan pills, you know, for certain pharmaceutical companies. It varied by -- by pharmaceutical company.

BY MR. VAUGHN:

Q. Which pharmaceutical company had the highest levels of NDMA in their Valsartan?

A. I believe that it was the -- the defendant company.

Q. The ZHP?

A. Yes, I believe so.

Q. Do you know if ZHP's internal testing showed levels of NDMA higher in Valsartan than the FDA was aware of?

MS. ROSE: Object to the form.

THE WITNESS: No, I was not privy to, you know, internal company documents or reports, you know, in formulating my specific causation for this -- this -- this case.

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BY MR. VAUGHN:

Q. Do you know if any of the Valsartan pills that Mr. Roberts ingested had higher levels of NDMA in it than the FDA was aware of?

MS. ROSE: Object to the form.

(Whereupon, Daniel Nigh joined the deposition.)

THE WITNESS: I understand that, you know, Mr. Roberts' alleged exposure in some of the NDMA-contaminated Valsartan pills is above the FDA threshold limit.

BY MR. VAUGHN:

Q. It's a- -- they're all -- it's al; above the threshold limit.

But are you aware if any of his pills had more NDMA in it than the FDA even realized was in any of the Valsartan pills?

MS. ROSE: Object to the form. And it's going outside the scope of his expert report.

THE WITNESS: Yeah. Like I said, I'm not privy to, you know, internal company documents from ZHP related to what they did or did not know related NDMA content in their pills.

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So I -- I don't know about that. I haven't reviewed those, you know, pertaining to specific causation for Mr. Roberts.

BY MR. VAUGHN:

Q. My question, though, is specific to Mr. Roberts.

Are you aware if any of the pills that he ingested had more NDMA in it than the FDA thought was the highest levels in Valsartan?

MS. ROSE: Object to the form. And again, this is outside the scope. What the FDA knew or thought --

MR. VAUGHN: If he wants to give an opinion on the risk level that the FDA is saying, then it is relevant.

MS. ROSE: I -- I don't think that's what he's saying, but okay. I -- I -- just don't see how he has any knowledge of this or is offering any opinion.

MR. VAUGHN: Then he can say he has no knowledge. That's fine if he says he doesn't know.

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THE WITNESS: Yeah. And I mean, that's what I've stated. I'm not privy to these documents. I have no knowledge of that. I know what's been reported in terms of the range of NDMA con- -- you know, contamination. That was potential -- potentially identified in those Valsartan pills.

If there was some internal company documents, you know, stating that there was potentially higher exposures, I'm not privy to those documents. I haven't reviewed those.

BY MR. VAUGHN:

Q. Okay. Earlier in your answer, you said, "I understand Mr. Roberts' alleged exposure to some NDMA-contaminated Valsartan pills."

What do you mean by "alleged exposure"?

A. The exposures that are -- you know, there's -- I say alleged because there's uncertainty in the actual dose exposure of NDMA in a particular pill.

You know, I think we acknowledge

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that we don't know specifically what the dose was that he was exposed to, nor do we necessarily know, you know, to what extent he's adherent with medications. There are variables that impact our assessment of what his actual dose exposure was.

I don't deny that he filled prescriptions for Valsartan that were NDMA-contaminated based on, you know, the batch lots and things like this. But I don't -- I can't -- there ' a lot of uncertainty in terms of what is his actual cumulative dose exposure.

Q. And ZHP's counsel didn't provide you with any calculations that ZHP did on what those does levels would have been in those pills?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. You know, the answer's the same. I don't have any internal, you know, company documents related to, you know, what they -- what they thought the NDMA levels were in their pills. Only what --

BY MR. VAUGHN:

Q. If those --

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A. Sorry.

Q. If those levels existed for the pills that Mr. Roberts actually ingested, is that something that you would want to see in coming to your opinions?

MS. ROSE: Object to the form.

THE WITNESS: So, again, my honest impression of this case is it really would not materially change my opinion and conclusions about the case.

You know, I think I have -- you know, there's very clear reasons in my opinion why, NDMA, even if he had hypothetically been exposed to higher doses, could not have been the cause of his hepatocellular carcinoma.

So I don't think it is necessarily relevant to the scope of -- of my role as, again, not a toxicologist. I'm commenting -- commenting on the plausibility that NDMA-contaminated Valsartan could have been plausibly been the factor that caused Mr. Roberts to develop HCC.

My opinion does not actually

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change depending on even if he was exposed to a higher dose. There are very clear reasons why it could not have been the NDMA.

I'm happy to articulate that in more detail if you'd like, but it's in my expert report, of course. But even if I had that data, it would not change my opinion.

BY MR. VAUGHN:

Q. So regardless of how much NDMA Mr. Roberts was exposed to, it wouldn't change your opinion?

MS. ROSE: Object to the form. Misstates the witness testimony.

THE WITNESS: Yeah. What I'm relying on is, you know, my opinion is he likely already had hepatocellular carcinoma when he was first exposed to NDMA. I -- I provide some very clear evidence of this in my expert report. You know, there's multiple ways of looking at this.

But among them are just looking at very simple tumor volume doubling times.

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You know, we talked about the stage of cancer that he was diagnosed with. It's really important to highlight that when he was diagnosed in, you know, April -- you know, July/April of 2018, he did not have early stage hepatocellular carcinoma. He had multiple lesions. There were two lesions that were clear -- clearly LI-RADS 5 lesions that were, you know, HCC, the largest of which, from my recollection, was 5.8 centimeters in diameter.

You don't get a 5.8-centimeter diameter HCC overnight. That does not occur quickly. That takes a long time to get there, to that size. And fortunately, this is something that's been studied in great detail across many studies. There's a lot of interest in understanding growth rates of HCC so we can understand what to expect in patients and how to prognosticate.

And in my expert report, you know, I cite the literature, and I give the different ranges, the average tumor volume

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doubling time, the extreme cases of very aggressive growth and -- and very slow growth. And I ran simulations for all of those.

And no matter what assumption you take, even if I assumed the most aggressive form of hepatocellular carcinoma with the fastest growth rates that are observed in -- in -- you know, in multiple observational studies, Mr. Roberts would have already had HCC in his liver prior to the time he was first exposed to NDMA-contaminated Valsartan.

So there's no plausible way you can say that NDMA, regardless of the dose, could have caused it if it's already there. So the temporality is -- is a really key point in this case and one that we didn't really talk about explicitly.

But I have to highlight it in the context of this to explain why my opinion doesn't change. Even if he had, hypothetically, had a higher dose exposure to NDMA, my view is that his cancer was already there.

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BY MR. VAUGHN:

Q. Understood. And I was planning to get to it if we had time in the deposition.

What's the fastest growth rate for HCC?

A. Yeah. So, you know, we look at this mostly in terms of tumor volume doubling time. I'm pulling up my report to give you very precise numbers.

Okay. So tumor volume doubling time, again, these are -- these estimates are aggregated. It's actually coming from a meta-analysis of many different studies to get as accurate of representation of the range of growth rates as possible.

The most -- so if you take the 95-percent kind of confidence interval in terms of one extreme to the other, the most sort of aggressive growth rates are on the scale of 3.9 months for tumor volume doubling time.

And so I have table where I kind of go through these calculations. The average is about 4.6 months for tumor volume doubling times, and the slower one are 5.3 months of tumor volume doubling time.

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Q. So 3.9 months is the quickest doubling time of HCC?

A. Tumor volume doubling time, yes.

Q. Is it your opinion that NDMA cannot cause cirrhosis?

A. So I think, you know, in -- in animal literature, you know, at a sufficiently high dose, you know, I do think that NDMA can likely cause hepatic fibrosis and likely cirrhosis, you know, in, you know, rodent studies, for instance. But I don't think that's been demonstrated to any sufficient degree in humans.

Q. Did you search for that?

A. Yes.

Q. What -- where -- what did you search?

A. Yeah. So I had a range of different searches. You know, I looked for, you know, NDMA, you know, liver fibrosis, liver, obviously hepatocellular carcinoma. I looked, you know, nitrosamine, you know, liver cirrhosis, hepatocellular carcinoma.

I did this specifically because in the -- the plaintiff expert witness report, she

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made the claim that NDMA could have caused the cirrhosis. So I -- so I did look into this specifically. Obviously, I first started in the context of NDMA-contaminated Valsartan to try to be as specific to the case as possible, and then, you know, when I didn't really find any scientifically compelling evidence that NDMA-contaminated Valsartan could plausibly cause cirrhosis, I -- I broadened my search to look at different nitrosamine-related studies.

Q. And on page 20 of your expert report, you said there's no scientific evidence to substantiate that NDMA is a cause of cirrhosis, correct?

A. All right. Page 28, you said?

Q. Page 20. Here. I can screen share to help you?

A. I'm just trying to find the exact quote.

Q. There we go. Right here: "No scientific evidence to substantiate NDMA causes cirrhosis."

A. Yes. And it -- the context here I'm referring to -- she's talking about in the context of Mr. Roberts' HCC. So implicit here

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is that I'm talking about the context for a human patient.

Q. Okay.

A. Yeah.

MR. VAUGHN: Kathryn, can we do 2023 United States Health and Human Services. This is going to be Exhibit 17.

(Whereupon, Exhibit 17, Document titled, "Toxicological Profile for N-Nitrosodimethylamine (NDMA)," dated April 2023, was marked for identification.)

MS. AVILA: It should be in there now.

MR. VAUGHN: Okay.

BY MR. VAUGHN:

Q. All right. Doctor, this is an April 2023 toxicological profile on NDMA that was put out by the United States Department of Health and Human Services along with the Agency for Toxic Substances and Disease Registry.

Have you seen this document before?

A. Yes, I have seen this before.

Q. And when -- when did you see this?

A. I believe I saw this -- you know,

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I -- I think I may have scrolled through again sometime in the past, probably, ten days.

Q. Did you see it before you came to your expert opinions in this case, before you submitted a report?

A. Yes, I -- i believe I reviewed this, you know, as well as other kind of, you know, kind of regular, you know, documents from other large institutions like the WHO, IARC. I reviewed a lot of that initially in the context of writing my expert report, but I did take another passthrough of elements of this probably, like I said, in the last ten days or so.

Q. And did you see any evidence in here that NDMA would cause cirrhosis?

A. You'd have to point me to specific areas to refresh my memory. It's hard to keep track of what was in which document, but...

Q. No problem. Let me see.

A. Yeah. I appreciate that.

Q. All right. So it's -- PDF page 41 is where I'm at, where it's talking about hepatic.

And "hepatic" means liver, correct?

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A. Yes.

Q. Okay.

A. I'm sorry. You said -- 41, you said? Oh, I'm sorry. 40 -- PDF page 41.

Q. That's where I'm at now. Sorry. That's where it starts on hepatic. That's where it starts talking about this study called Hidajat.

You're familiar --

A. Yes --

Q. -- with Hidajat?

A. Yes.

Q. Okay. If we go down here first, it's talking about -- one second.

So there's a case of automobile factory workers who were exposed to an unknown level of NDMA, and they became violently ill with jaundice.

And they talk about some other ones. Five family members who consumed unknown quantities of NDMA and became -- in limine and became ill with nausea, vomiting, serum changes associated wit acute liver disease, as well as bleeding and slight-to-severe thrombocytopenia.

Do you see that?

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A. Uh-huh. Yes, I see that.
Q. These are humans that it's talking about, right?
A. Yes. I do remember reviewing these. Thank you for showing me because I -- I recall these. Again, these are case reports from a long time ago. You know, from the '70s and the '80s. I think I may have reviewed more than these.
And I recall another case report where someone had a toxic exposure to NDMA and likely other things, and on the autopsy there was cirrhosis. I remember seeing a report along those lines as well.
So yeah. I acknowledge that those are humans that have been reported, but the issue again, you know, with case reports and case studies is that there's no ability to assess associations or magnitude of risk factors. There's no accounting of potential biases or -- or limitations.
It's -- it's purely reporting through the lens of -- of the provider or whoever's running the case report, a series of events. They say that someone had NDMA

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exposure. Later they were found to have cirrhosis on autopsy or, you know, or they became ill. They were found to have jaundice.
We know nothing about whether that's attributable to NDMA. We know nothing about, you know, whether or not they had preexisting cirrhosis or if they had significant alcohol use that led to cirrhosis, if they were taking other substances in addition to being exposed to NDMA.
So you have to be very, very cautious in trying to translate something from a case report. And this is a theme I keep highlighting. But this is not compelling scientific evidence to establish causality in my view as a clinician -- scientist and a clinician between NDMA exposure and -- and cirrhosis.
So that -- that's my view about these case reports. But yes, I've reviewed these. I've seen these case reports as well as others.
Q. In your expert report, you said there's no scientific evidence.
There's scientific evidence. You

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just don't think it's strong enough, correct?
MS. ROSE: Object to the form.
THE WITNESS: I believe what I state is there's no scientific evidence to substantiate the claim. So what I'm referring there is there's no -- there's no -- there's no -- there's no evidence in the literature of sufficient quality to make a causal claim in humans between NDMA and cirrhosis. I'm not --
BY MR. VAUGHN:
Q. And you agree -- sorry.
A. That's good.
Q. And you agree that you can't give it to humans intentionally to study it, correct?
A. Yes, I would agree with that.
Q. And so would there ever be enough evidence for you for this association if you can't actually study it in humans?
MS. ROSE: Object to the form.
THE WITNESS: So it is possible, I think, to do a very high quality study using, you know, high quality causal inference methodology that, if

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demonstrated consistently across multiple studies, that -- that I think could make a sufficient -- could meet a sufficient standard of evidence to make that claim. My opinion, though, is that we don't have such literature in humans to make that claim.
But -- but yes. It would not require a randomized trial. I mean, I acknowledge that it would not be ethical to do a randomized control trial in humans. So we are reliant on observational studies, but you have to look at quality of individual observational studies and measure those very carefully when you're making this adjudication of is a causal inference warranted both generally and, of course, as applied specifically in this case to Mr. Roberts is what my -- my primary concern is.
BY MR. VAUGHN:
Q. And do you see on the next page where, then, United States Health and Human Services talks about two men who got liver

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cirrhosis after just using NDMA in a research laboratory?

A. Yes. I think that's probably what I was referring to when I was talking about the case where on autopsy, you know, the case reports where there was an NDMA exposure, and then on autopsy there was cirrhosis.

But like I said, we don't know if that cirrhosis was already present. Those -- those individuals could have already had cirrhosis from a multitude of different causes. They happened to take NDMA in very, very high doses or potentially other exposures in addition to NDMA. And -- you know, and then it might be an incidental finding on the autopsy that there is cirrhosis.

There's no ability to directly attribute causally that the NDMA in a case report was the reason that these individuals had cirrhosis. It's just not possible to make that claim.

Q. Okay. That's the same thing you're saying for Mr. Roberts is he already had cirrhosis, so it couldn't have been NDMA that caused it, right?

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MS. ROSE: Object to the form.

THE WITNESS: Well, I'm saying multiple things. I'm saying from the scientific literature, I don't even know if it's -- there's not in any evidence in the scientific literature to -- to demonstrate that it's -- it's -- it's -- it's causally linked at all in humans, certainly at that relevant dose exposure, to cause cirrhosis in humans. So that evidence standard is not met.

But certainly in the specific case of Mr. Roberts, as you know, it's very clear that he already has cirrhosis at the time he's first exposed. So obviously, the NDMA could not have been the cause. I mean, the cirrhosis was antecedent to his first NDMA exposure.

BY MR. VAUGHN:

Q. How much NDMA do you think someone just in the lab doing research would actually be exposed to?

MS. ROSE: Object to the form.

THE WITNESS: There's no way for me to -- to know. I don't know. This is,

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like, from the 1950s. I don't know what type of research laboratory they worked in.

Like I said, I'm not a basic scientist, so I have no idea what the specific context of this research lab was. So I don't know. I don't know what the plausible range was in that, and they don't seem to specify it here.

And I think the other case study you mentioned on the page that said an unknown quantity of NDMA. So it may not even be known.

But again, these are extremely old case reports, and you have to be very skeptical of particular very old case reports where the quality of the data and the reporting or what could have been a adjudicated or identified was more -- more limited back then.

So it's really, really difficult to really find -- find anything that's really concrete and useful from, you know, a 1954 case study.

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BY MR. VAUGHN:

Q. Do you know why people research NDMA in the laboratory setting?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I mean, in the laboratory setting, you know, as I've already -- I mentioned and I understand, and I concede that in animals, you know, it -- it's demonstrated that NDMA in very high doses can cause hepatic fibrosis, can cause different types of liver cancer, not just HCC, but bile duct cancers as well.

And so it's studied in that context for itself carcinogenicity in animals and to help justify -- or I suppose it helps to justify human studies to explore that potential relationship more as potential effects in humans.

BY MR. VAUGHN:

Q. And do you see here where they say, "The patient showed improved liver function after three months with no exposure to NDMA"?

A. Sorry. Yeah. So I mean, this is another thing that makes me a little bit skeptical of this case report from 1954 where

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they say that cirrhosis was discovered during operate, and -- and there was improvement in liver function.

I don't know what they mean by "liver function." I'm not sure what labs they're referring to or on what basis they're saying that liver function was improved.

As I said before, you know, cirrhosis is generally considered to be binary. You know, if cirrhosis is there -- if cirrhosis is there and you manage the patient as such.

So without kind of revisiting that study in more detail to see on what basis they're saying that, I don't necessarily know what they're referring to; but I'm skeptical for those reasons.

Because certainly once there's cirrhosis present, there's already a state of liver injury that is ir- -- you know, generally irreversible. So -- so I'm not sure what they're referring to there.

Q. Do you see here where the United States Health and Human Services says, "Hepatotoxicity is the most prominent characteristic systemic effect of NDMA

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resulting in" -- what is this?

Central lobular necrosis?

Did I say that right?

A. Yeah. Central lobular necrosis.

Q. -- "and hemorrhage, fibrosis, cirrhosis, and ascites."

Do you disagree with the United States Health and Human Services on that?

A. So let me take a look.

This is page 42, right?

Q. Uh-huh.

A. Yeah. So this again, you know, the preceding sentence is saying this is animal species. So in several animal -- so again, this is from the animal literature.

And no, I don't disagree with that from the animal literature. As I've stated, I recognize that high-dose NDMA, you do see these changes in rodents of liver injury, liver fibrosis, and the attendant complications, including HCC.

You know, but my -- my broader point is that there -- you have to be very cautious in translating animal study findings to humans. And there's, you know, not that you

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really are questioning, but it's very much related to this, that I have to emphasize that all of these animal studies study animals that have normal livers at baseline. They're exposing normal healthy, you know, rodents or whatever animal model they're using. They have a healthy liver. They're given high-dose NDMA, and they observe what happens.

It's important -- it's important to recognize that that is not analogous to Mr. Roberts' case. He already has cirrhosis. Why is that relevant?

If you look at Sawyer's expert report, he talks about the mechanism of carcinogenesis attributable to NDMA.

NDMA needs to be activated in the liver. It needs to be metabolically activated by enzymes in the liver to toxic metabolites. The NDMA itself is not the issue. It's the toxic metabolites.

That's important because if you have a liver that already has cirrhosis, it is not effective. It is not as effective as a healthy liver in metabolizing NDMA to the toxic metabolites. This is another principle that we

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understand as hepatologists that's very relevant because we actually change the way we prescribe certain medications if we think cirrhosis is present. If cirrhosis is present, it will not reliably metabolize things.

So there is a highly plausible reason to expect that even if, hypothetically, you know, I were to grant that there is, you know, some concern that NDMA could cause liver cancer in humans, which, again, I don't grant based on the scientific literature we talked about, there's no reason to believe that that would apply to somebody who already has cirrhosis who's unable to reliably metabolize NDMA to the toxic metabolites. There's literally no data in such a patient, animal or human, where they've studied NDMA exposures specifically in a baseline cohort of animals or humans who already have cirrhosis. So --

Q. So it's your -- keep going.

A. That's fine. That's good.

Q. So is it your opinion that Mr. Roberts is at less risk to NDMA because his liver's not functioning as well?

MS. ROSE: Object to the form.

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THE WITNESS: What I'm saying is that even the animal literature doesn't apply to him. I mean, it's -- it's -- it's another cautionary tale of why you can't blindly translate animals studies to humans. There are other independent reasons for that.

But specifically bringing it back to the case of Mr. Roberts, he has cirrhosis at the time he's exposed to NDMA; and there's literally no relevant literature that I'm aware of, animal or otherwise, where they look at NDMA exposure in the setting of organisms that already have cirrhosis.

So we don't know really anything at all about what to expect in those patients.

BY MR. VAUGHN:

Q. And for the mechanisms of hepatoxicity of NDMA, the United States Health and Human Services discusses how NDMA was given to both dogs and rats and has been used as a model for human liver fibrosis and its sequelae of cirrhosis, portal hypertension, and

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hepatocellular carcinoma for nearly 40 years.

And so do you -- you disagree that dogs and rats can be used as a model for human fibrosis with NDMA?

MS. ROSE: Object to the form.

THE WITNESS: So no, I don't disagree that animal models are used in -- in this fashion, you know, all the time.

The part that I'm trying to clarify and demonstrate my disagreement is that you cannot blindly translate findings from animal research to humans. You need dedicated humans studies, which often take time and long-term follow-up to demonstrate that the same things are observed in humans.

I mean, this is a very, you know, well-known phenomena called the translation -- translational gap. You're not guaranteed to see the same things in animal studies as human studies. I mean, there -- there are very famous prominent examples that serve as cautionary tales for doing just that.

So yes. In the lab, sure, we use

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these as, you know, the best available model for what could potentially happen in a human; but that doesn't absolve researchers and scientists and clinicians from doing the requisite research and work in humans specifically to see if that translation is warranted.

BY MR. VAUGHN:

Q. In the Health and Human Services there has been a great deal of research performed to investigate the molecular mechanisms and pathophysiology of NDMA-related hepatic effects. George, et al. 2019 published a succinct review of this research.

Did you review George, et al. 2019 in coming to your opinions in this case?

A. I mean, I reviewed a variety of literature related, you know, from the -- this is again from the animal literature.

Q. Uh-huh.

A. So -- so yes. I reviewed a variety of different studies that -- that discuss the -- the -- the mechanisms of hepatoxicity and carcinogenesis of NDMA and animal studies.

I don't -- I can't immediately

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recall if George, et al. is one of them, but I'm certain I reviewed, if not that one, then closely related ones that talks about this.

Q. Okay. Because Dr. Siddiqui listed that as one of her materials considered when she was --

A. Okay.

Q. -- saying that NDMA could cause cirrhosis in humans. And you said she had no scientific support for that.

Do you retract that statement?

MS. ROSE: Object to the form and colloquy.

THE WITNESS: No, I don't retract that statement. Again, my statement is that there's no -- there's no, you know, substantiated literature in humans to demonstrate that NDMA is causally linked to cirrhosis, you know, in studies that are scientifically and methodologically sound with sufficient effect sizes and power, et cetera, to -- to demonstrate that conclusively.

So I stand by that statement. And I think, you know, if you want to talk

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about George, et al., I think you'd have to show it to me again just to jog my memory.
BY MR. VAUGHN:
Q. Okay. So it's not necessarily that there's not any evidence at all out there. It's just not good enough evidence for you, correct?
MS. ROSE: Object to the form.
THE WITNESS: Yeah. I think I've articulated that a couple of times that, you know, the human literature that is -- that is purporting to associate NDMA with something like cirrhosis, they're based on case studies that are from, you know, 80 years ago, 70 years ago, where you cannot systemically study NDMA as a risk factor because they're not analytical studies. So no. That is -- that is not a valid way to determine a risk factor.
Really no clinician who understands what a risk factor is would rely on that as evidence to say that NDMA causes this. You need much more high quality evidence to demonstrate that.

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BY MR. VAUGHN:
Q. So you just think there's insufficient evidence of NDMA causing cirrhosis in humans?
MS. ROSE: Object to the form. Asked and answered.
THE WITNESS: I mean, I can restate the same thing I said. I mean, to my standard, which I think is a commonly held standard for, I think, reputable clinicians and clinician scientists, you want to see high quality medical literature that is an analytic study, right. So not descriptive analytic. These are high quality observational studies, for instance, or interventional studies, which I agree we can't do in this setting, to demonstrate using causal inference methodology that there is a strong and consistent effect that's observed between NDMA and cirrhosis. And we don't have that.
BY MR. VAUGHN:
Q. Were you aware that NDMA degrades into formaldehyde in the human body?

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A. Yes.
Q. Okay. And is formaldehyde a potent hepatotoxin?
A. Formaldehyde I believe in, you know, sufficient concentrations can be -- yeah, it can be a toxin. Yeah, absolutely.
Q. And at what -- and at what concentration of formaldehyde would you need?
A. I couldn't give you a number off the top of my head.
Q. Okay. And do you see here where it's talking about initiating events leading to hepatic fibrosis in NDMA-exposed organisms? What -- what's an "organism"?
A. An organism is a living -- it's a, you know, an animal is an organism. A human is an organism. It's a living -- it's a living entity, I suppose.
Q. Okay. So United States Health and Human Services thinks that NDMA and its degradant such as formaldehyde can end up leading to hepatic fibrosis in NDMA-exposed humans, right?
MS. ROSE: Object to the form.
THE WITNESS: So, you know, they're

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not specifying which organisms here. They're not being very specific. So I mean, this may have been from primarily animal literature. I'm not certain. They would have to be more specific and probably cite specific references to clarify what they're saying.
BY MR. VAUGHN:
Q. Okay.
A. Organisms is an extremely broad term.
Q. All right. Can you name me one study in which NDMA has been studied in an animal and was not carcinogenic, one animal, one organism?
MS. ROSE: Object to the form.
THE WITNESS: I mean, off the top of my head, I -- you know, I don't think all the animal studies with NDMA exposures look at that specifically as an end point. I mean, there are -- are I think quite a few animal studies where they're looking at other types of cancers, for instance.
So, you know, perhaps what you're asking is in animal studies where they're

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intending to study specifically liver effects, I -- you know, I can't name off the top of my head any specific study, you know, to my recollection that did not identify, you know -- you know, some association with hepatic fibrosis or liver cancer with, you know, high-dose NDMA exposure.

BY MR. VAUGHN:

Q. And so is it your opinion that humans are the only organisms that aren't going to have hepatic fibrosis as a result of NDMA exposure?

MS. ROSE: Object to the form.

THE WITNESS: No. That's not my opinion. I mean, this -- this has been studied in, you know, selected types of organisms; but it's not studied to this degree, you know, with sufficient evidence at the dosing ranges in particular that are used in animal studies. There's no demonstration that, you know, that we would necessarily see the same thing in humans.

So I'm not -- I'm not saying that

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it's not possible that in the future a well-conducted study could -- could demonstrate some potential link between NDMA and some adverse, you know, related event. That's possible. It's possible to do a very high quality study.

What I'm saying is there's no evidence currently in humans that demonstrates this. So we, therefore, can't make the conclusion for Mr. Roberts that -- that this could be causally linked.

I mean, this, again, setting aside the temporality issues that I've stated previously that -- that they clearly, you know, articulate why it could not have been NDMA. But based on this line of questioning, that's -- that's what I'd say. There's insufficient human evidence to demonstrate this.

BY MR. VAUGHN:

Q. Do you see here where the United States Health and Human Services said, "In addition to the DNA damage induced by reactive intermediaries [sic] of NDMA metabolism,

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repeated injury and repair induced by these metabolites may also be involved in the mechanism of liver cancer from NDMA exposure."

Did I read that correctly?

A. You read that with one word -- I think you might have misstated intermediates. I think you said intermediaries.

Q. Thank you.

A. That's okay. But aside from that word -- word, yes, you read correctly.

But when I read this, this -- I feel like this really substantiates a lot of what I've been saying kind of throughout the deposition.

So one thing that's immediately clear -- immediately clear from this statement is the DNA damage induced to animal studies is from the reactive intermediates of DNA metabolism.

Farther up the page, you know, if you scroll through, it talks about how the liver and the, you know, the esthetic P chrome 50 system is the mechanism by which NDMA gets processed and metabolized into these toxic intermediates, including formaldehyde and, you

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know, methyldiazonium and others.

So that's -- that's an important point, which is why I highlighted that it takes a healthy liver to do that. And if you have cirrhosis, your liver is not healthy. You do not have normal metabolic activity. We don't even know if a -- if a cirrhotic liver could actually metabolize NDMA to those reactive intermediaries. So that's one important point.

The second point from this sentence is that the repeated injury and repair induced by this, this gets at what Sawyer's talking about with respect to promotion. He talks about inducer and promoter. The third face of carcinogenesis is -- is progression.

The promoter part of this requires repeated chronic long-term exposure to a carcinogen in order to develop cancer. So the repeated injury part's actually very important because the time scale is relevant. And as I stated previously, you know, a two-year exposure to a potential carcinogen is generally not anywhere close to sufficient to causing a solid tumor in humans. That would be really extraordinary. I can't think of a -- of a case

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where I've ever seen that. I'm not saying it's totally impossible, but that would be far outside the bounds of what is generally observed with toxic exposures and latency periods for cancers.

And the Hidajat study you mentioned previously -- I know we didn't talk about it in detail -- but on -- to the credit of the authors of Hidajat, they understand this. They use an appropriate latency period in their study of 15 years from NDMA potential exposure to looking at cancer-related mortality.

They understood that if somebody had a toxic exposure to NDMA and they got a cancer five years later or ten years later, they could not plausibly associate that with the NDMA. It's just not what is observed with the pathway of carcinogenesis.

So the repeated injury part there is really, really important, and the chronic exposure needs to generally be sustained for, you know, for a long period of time. And years and years and often decades go by before a cancer develops.

So -- so I take something very

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different away from the sentence than it sounds like you're implying; but to me, those are the really important things to -- to drive home.

MS. ROSE: Mr. Vaughn, we've been going for over an hour.

MR. VAUGHN: I'm close.

MS. ROSE: Okay.

BY MR. VAUGHN:

Q. So you don't consider, you know, 600-plus doses of NDMA at microgram levels to be a repeated injury to someone's liver?

A. I agree it's a repeated exposure. The point I'm articulating is even if I were to grant that those doses -- that dose range in a human could be plausibly linked to a potential cancer, in my view that is not a sufficient latency period for a cancer to develop, for carcinoma to development. That's my -- that's my position.

Q. And based on what you were saying earlier, it's your opinion that someone with liver disease is at a decreased risk from NDMA exposure?

MS. ROSE: Object to the form, and also asked and answered.

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THE WITNESS: Yeah. I mean, again I'm -- I'm -- I'm -- I'm not -- you know, I'm talking mechanistically based on what has been defined in the animal literature, right.

So the animal literature has done a great job of studying the potential mechanisms of hepatotoxicity and carcinogenesis. And it's very clear -- and I don't think it's disputed by really anybody in this case -- that the way in which NDMA is carcinogenic in animals is that NDMA gets metabolized in the liver through the cytochrome P450 enzymatic pathway to toxic intermediates that then cause things like DNA, you know, alkylation that increase the rate of DNA mutations, et cetera, and sets off this cascade, which, again, takes a long type.

If you -- if you -- if you just understand what that mechanism means, it necessarily entails that you have a functioning liver to metabolize the NDMA.

This -- I mention that, you know, hepatologists, we have to think about this

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when we dose medications. Patients with -- just a very brief articulation of this if it's okay.

Patients who have, you know, alcohol -- well, probably a better example, patients who have autoimmune hepatitis, it's one of the potential causes of cirrhosis, we typically treat those patients with an immunosuppressing agent called Prednisone.

Prednisone needs to be activated metabolically in the liver to prednisolone, which is the active metabolite that actually suppresses the immune system and helps to manage autoimmune hepatitis.

When a patient with autoimmune hepatitis has progressed already to cirrhosis, we don't use predni- -- Prednisone anymore. We use prednisolone because we can't rely on the liver metabolize to prednisolone, which is the active intermediate.

The same principle applies with -- you know, if this is the mechanism that's

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hypothesized in demonstrated animals, if we try to translate this to humans and we assume that the same things would apply in humans, you wouldn't need a functioning liver to metabolize NDMA to a toxic intermediate.

So -- so yes, it's very plausible that a patient would cirrhosis would actually be relatively protected from, you know, NDMA-related toxicity if, in fact, that were to exit.

BY MR. VAUGHN:

Q. You say it's very plausible.

Do you have any scientific evidence specific to NDMA on that opinion?

A. I don't because, as I -- as I've stated numerous times, there's really limited -- there's no data in patients with cirrhosis in humans being exposed to NDMA or in animals with preexisting cirrhosis.

Q. Okay. Let's go to page 94 of this.

Do you see here, "Other factors influencing susceptibility"?

Read the sentence out loud to the jury from the United States Health and Human

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Services.

A. Sorry. I'm scrolling to 94.

Q. I have it highlighted if that's easier for you.

A. Okay. Sure.

MS. ROSE: The doctor should -- if you'd like to look at the document, you can look at the document.

THE WITNESS: Yeah. I just want to get a sense of the context really quickly to understand what the -- what they're talking about here.

BY MR. VAUGHN:

Q. It's under the bolded heading "Other Factors Influencing Susceptibility."

A. Sure. I see it.

Q. All right. Can you read the highlighted sentence from the Health and Human Services?

A. Sure. So it says, "Other factors influencing susceptibility. Because the liver is the primary target of NDMA toxicity, individuals with liver disease may be at increased risk factors from NDMA exposure."

MR. VAUGHN: We can take a break

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now, Nina.

THE VIDEOGRAPHER: Off the record at 5:14.

(Whereupon, a break was taken.)

THE VIDEOGRAPHER: We are back on the record at 5:27.

BY MR. VAUGHN:

Q. All right. Doctor, I want to go back to your expert report, which is Exhibit 1, and I'm going to be on page 33 to start with.

A. Sure.

Q. For your tumor doubling time that you were talking about earlier, you cite to, I believe, it's Nathani Number 95. Let's see here.

95 is Nathani, correct?

A. Yes.

Q. Okay. And when you were doing this calculation -- can you explain this calculation real quick to me, what you're doing, how it works for tumor volume doubling time?

A. Sure. So I'm using a method that's are commonly used in these studies where they study tumor volume doubling time.

But basically, you start with the

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assumption that a tumor is roughly spherical. So the first thing I'm presenting there is the formula for the volume of a sphere. So V is -- is volume. That's equal to one-sixth times pie times D cubed where D is the diameter. So that's the first part.

The second part I'm just rearranging and solving for D, which, again, is diameter. Because oftentimes, you know, we don't typically report the volume of a tumor on a radiology report. We measure things in terms of diameter.

So that's why, you know, for instance, on Mr. Roberts' imaging reports they say, you know, the tumor 5.8 centimeters in diameter.

So that's why I'm trying to solve this to put everything in terms of diameter to make it more translatable to what you would see on imaging.

Q. Why is it that you have to assume the spherical shape?

A. Yeah. You have to make certain assumptions. Obviously, it's possible for -- that tumor's not going to be a perfect sphere.

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It might be, you know, a little bit lobulated and -- but you have to make assumptions -- for the purposes of just doing the studies, you make the assumption.

They typically are roughly spherical. If you look at tumors, they tend to -- just the way they grow, they grow in all dimensions, and they tend to grow roughly in an spherical shape. But, you know, I acknowledge that that's an approximation that we use.

And, you know, we make approximations like this in a lot of areas in medicine to help us understand biological and pathophysiologic processes.

So but I like I said, this is a -- this is a fairly standard assumption that's used in this type of literature for, you know, tumor volume doubling time.

Q. And so you're making the assumption that it was spherical when it started the cancer, and then it remained spherical throughout it's progression, correct?

MS. ROSE: Object to the form.

THE WITNESS: Yeah. I'm -- I'm -- yeah. Right.

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So I'm basically -- to do these calculations, to simplify the calculations and make things easily translatable, I'm making the assumption that the tumors are roughly spherical, yes.

BY MR. VAUGHN:

Q. And did you review the imaging in 2018 of Mr. Roberts' cancer?

A. Yes, I did.

Q. And was his cancer spherical?

A. I -- I would have to look at it again in detail. It's sometimes very tough to assess because we -- you, oftentimes, may need a good three-dimensional reconstruction of an image, a CT scan or an MRI.

You know, we look at it in terms of slices, typically, you know, in a coronal or a sagittal or a transverse axis. And, you know, we -- I was not presented with any of the three-dimensional reconstructions. So it's -- it's tough for me to be able to say confidently is it -- is it spherical or is it not spherical.

I doubt it's perfectly spherical; but like I said, this is an assumption that is

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commonly used in these studies to help us understand and approximate tumor volume doubling time.

Q. And so you're assuming that Mr. Roberts' liver cancer was also spherical, correct?

MS. ROSE: Object to the form.

THE WITNESS: For the purpose of these calculations, you know, I'm assuming that, you know, if Mr. Roberts' had a 5.8-centimeter diameter tumor, for the purpose of calculations, I'm assuming it's roughly spherical.

I'm not saying that in actuality, it was a perfect sphere. But, you know, to approximate doubling time, we -- we make an assumption that's sphere. You know, the formula you have to try to put together to -- to accurately get the topography of an HCC mathematically would be, you know, extraordinarily complex; and it's -- for that reason, it's not typically done that way.

So yes. It's an assumption I make, but I think it's a very reasonable

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assumption. It's a very common assumption used in the medical literature.

BY MR. VAUGHN:

Q. And you note here "aggressive growth being 3.9 months," correct?

A. Yes.

Q. And where -- where did you get this definition that aggressive growth is a doubling time -- or doubling every 3.9 months?

A. So in this study that we talked about, Reference Number 95, they -- it's a meta-analysis of many different studies. I can't remember the specific number. It might have been roughly 20 studies, I think. Oh, yeah, it's 20 studies. I state it right there. Sorry.

Yeah. On page 33 I state that it's a meta-analysis of 20 different studies, that all were trying to estimate tumor volume doubling time. And what this study did was, it looked at the distribution of growth rates in tumor volume doubling times that were -- that were reported in those studies; and they created -- pulled estimates to arrive at a distribution. And that allowed them to

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compute, based on these 20 different studies, what is the average doubling time, and then what is the 95-percent confidence interval for that estimate.

And so what I'm, you know, just for simplicity, I'm describing the range. So if I take one extreme end, you know, the lower end of the 95-percent confidence interval, that was 3.9.

So that's, you know, on -- on the extreme end of this bell curve, that would be that growth rate, 3.9, you know, months for a tumor volume doubling time. That's what I'm calling aggressive growth because it's the fastest rate of growth on the distribution.

Whereas, on the other side, 5.3 is the upper bound of the confidence interval, which I'm referring to as slower growth. That's -- that's just a slower tumor volume doubling time.

Q. And so if it was doubling even faster than 3.9 months, what would you call that?

Would that be, like, super-aggressive growth?

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MS. ROSE: Object to the form.

THE WITNESS: Here I'm just using the word "aggressive" to make it very clear what I'm doing, that this from this study was, you know, on the extreme end of the distribution. So these were generally among the most rapidly growing tumors that were observed across all of these studies.

Sure. There are some tumors that are slightly beyond that, you know, maybe like the 97t, 98th, or 99th percentile would be slightly faster rate of growth than this. I'd refer to all of those as being aggressively growing tumors. That's very rapid for HCC to grow.

BY MR. VAUGHN:

Q. And you did your math here backing up the doubling time, and you come to 27.3 months. And so he was diagnosed with cancer in 2016.

So would 27.3 months be approximately April of 2016 when he had this imaging done?

A. Sorry. I'm just trying to think of the dates again.

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So he was diagnosed with HCC roughly, let's say, August of 2018, right.

So 27 months prior to that, yes, that's approximately when he had the -- the CT scan in April of 2016. That sounds about right.

Q. Okay. And so your calculation says that his tumor would have been 1.15 centimeters at March of 2016 -- April 2016, correct?

A. Yeah. Again, this is an approximation based on these formulas with these assumptions, yes. You'd expect that he -- he might have a tumor roughly in that size range. It might not be perfectly 1.15 centimeters. Obviously, there's some degree of error.

But the point is you would expect him, with all these assumptions, to have a lesion that is likely visible on imaging at that time.

Q. And he didn't have any lesions that were that size at that time in 2016, did he?

They were .6 centimeters, .5 centimeters, .5 centimeters, correct?

A. So yes, that's correct that they

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were not exactly 1.15 centimeters in size. But, you know, I've already acknowledged that we make assumptions; and there's some degree of slight variation in error that -- that can be expected for these estimates. So that's why I'm saying they're estimates.

It's possible that maybe he had a slightly more aggressive -- maybe he was in the 96th percentile. I -- I don't know.

But the fact is all the projections would predict that he had identifiable lesions on imaging, and he does. And moreover, you know, one of those lesions in particular is in the same exact location as, you know, his subsequent LI-RADS 5 lesion that's later seen and confirmed in his 2018 imaging.

So it's extremely -- it's plausible, and it's supported by this, you know, this -- this body of literature that has studied this in great detail. It's very consistent with his imaging findings.

He had identifiable lesions that were macroscopically visible. And sure I acknowledged that there's a margin of error in what the exact size is going to be, and that

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may be related to the fact that it's not a perfect sphere, as you have already stated.

But he had an identifiable lesion. And, you know, from Dr. Chernyak's expert report, she classified it as a LI- -- these are LI-RADS 3 lesions. These have intermediate probabilities at that time of -- of being HCC. And many of these LI-RADS 3 lesions over time will, in fact, declare themselves to be LI-RADS 5 lesions and cancer.

Q. And do you believe that these were LI-RADS 3 lesions, or were you just relying Dr. Chernyak?

A. I'm relying a lot on Dr. Chernyak's assessment here. Again, I'm familiar with the LI-RADS criteria, and I do look for them myself, you know; but, you know, like I said, I'm not a -- I'm not a diagnostic radiologist.

And in particular for the smaller lesions where some of the findings are more subtle, I'm more reliant on a diagnostic radiologist with relevant expertise to make this determination.

For me, it's -- I'm able to more confidently identify things like LI-RADS 5

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lesions where some of the features are a little bit more obvious to -- to my eye, you know, who doesn't, you know, look at, you know, MRI images every single day all day.

So for these particular lesions, I'm -- I'm more differential to Dr. Chernyak, but Dr. Chernyak has the relevant expertise. You know, she works in a liver transplant center. She's an abdominal diagnostic radiologist.

And so yes. If she classifies it as LI-RADS 3 and has the appropriate justification, I have no reason to doubt that.

Q. Is aggressive growth synonymous to rapid growth to you?

A. Yeah. So -- so my use of the word "aggressive" here, I'm -- I'm really just trying to -- I'm not trying to imply anything beyond the fact that it's more -- it's the fastest growth rate that I'm studying here informed by that -- by the literature that I've cited.

You know, I -- I'm not sure what your trying to get to with respect to, like, aggressive versus rapid. In this distribution,

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it's defined as an extreme value on the 95th percent -- from the 95-percent confidence interval.

So, you know, whatever adjective you use to describe it, I mean, that's what I'm referring to. So I'm giving you the very precise definition of what that is. It is the --

Q. I appreciate that.

A. Sure, sure.

MR. VAUGHN: Kathryn, can you drop in 2021 Nathani HCC tumor volume doubling time.

MS. AVILA: Yes, and it's Exhibit 18.

MR. VAUGHN: Thank you for that.

(Whereupon, Exhibit 18, Author manuscript entitled, "Hepatocellular Carcinoma Tumor Volume Doubling Time: A Systemic Review and Meta-analysis," by Piyush Nathan, et al., was marked for identification.)

BY MR. VAUGHN:

Q. All right. Doctor, and this is the study that you cited, right, by Nathani to

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2021?

A. Yes.

Q. Do you see here where the author defines rapid as a tumor double volume time of less than three months?

A. Sure.

Q. Okay. And that's not the timeframe that you applied, right?

You applied 3.9 months, correct?

A. Right. So what I'm -- what I'm doing is I'm taking the results of their studies.

You're highlighting something from the methods.

Q. Uh-huh.

A. If you look at the results of what they actually found in terms of tumor volume doubling times in the results section, you'll see that 4.6 months is the pooled average doubling time, with a 95-percent confidence interval of 3.9 to 5.3.

So that's the data that I'm using.

Q. Okay. And then on page 2, it does talk about how HCC, it has more aggressive patterns in Asians and Hep B populations.

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Mr. Roberts was not Asian and did not have Hep B, correct?
A. That's true. He did not have Hep B, and he was not Asian.
Q. Okay. Let me go to page 6 of this study.
Do you see down here -- earlier I asked you what the quickest time was for tumor volume doubling for HCC, and you testified 3.9 months.
Based on this study, do you see here where it's actually the quickest they note is 2.2 months for doubling?
A. Yeah. So I think I acknowledged that it's possible for things to be faster. I did say that it's possible that, you know, there can be doubling times that are beyond the 95-percent confidence interval bands. I acknowledge that.
But you look at the -- the range in the distribution of data to identify plausible scenarios. So yeah. I -- I acknowledge that it's possible for doubling time to be faster, sure.
Q. And did you model out what it would

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look like if it was doubling every 2.2 months in Mr. Roberts?
A. No, I didn't model that particular case. I modeled, again, based on the extremes from the distribution.
Q. And if it was 2.2 months, is the right way to do that, then, to be timesing [sic] 2.2 by 7 to figure out how many months earlier he would be at based on your calculations?
MS. ROSE: Object to the form.
THE WITNESS: That does not sound immediately accurate to me. I think you have to really apply this through the formulas that I laid out.
BY MR. VAUGHN:
Q. Can you see the expert -- can you see -- am I back on the expert report screen sharing?
A. Yes.
Q. Okay. Is 3.9 times 7, 27.3?
I can screen share a calculator if I need me to.
A. Sure. So it's 3.9 times 7. Yes, that's 27.3.

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Q. Okay. And 5.3 times 7, is that 37.1?
A. Yes.
Q. Okay. And so if the tumor volume doubling time was 2.2, would the accurate way to do that be to times it by 7?
A. Yeah. That appears correct based on what you're showing me, yes, yes.
Q. Which would be 15 -- which would 15.4 months?
A. Sure, 15.4 months.
Q. So --
A. But again -- sorry. Go ahead. Go ahead.
Q. So if he had the most aggressive form of cancer from that study, it would have started 15 months before his diagnosis, correct?
MS. ROSE: Object to the form.
THE WITNESS: That's not exactly correct. You'd actually have to extend -- let's see.
The issue is I think you may need to add more rows of data below this because there would be additional tumor

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diameters and additional rows on this table. They'd have to -- to model out to see what the diameter would have been at that time.
BY MR. VAUGHN:
Q. And does the tumor doubling keep going all the way to zero to the inception of the cancer, or does it stop being a valid formula at 1 centimeter?
A. That's a great question. I -- you know, I am not immediately sure, you know, to what -- what I'll say is things are very tough to macroscopically visualize on imaging when they're extremely small.
You know, when they're, you know, on the range of certainly less than .1 centimeters. Things are very tough to discern when they're extremely, extremely small.
So I presume that that could not be modeled accurately in these studies because you have to be able to measure it on imaging.
Q. What is the --
A. I think --
Q. Sorry.

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A. That's okay. Go ahead.
Q. What does the word "indolent" mean?
A. Sorry. Where are you looking?
Q. I'm not looking at the study.
Are you familiar with the word "indolent"?
A. Indolent. Yes.
Q. Indolent. Sorry.
What does that mean?
A. Yeah. Indolent generally means, you know, very slow growing or not -- you know, it's something on that spectrum. Not really -- not actively showing significant growth or very slow growing. That's usually how indolent is used.
Q. Can you see here in the study side where they talk about rapidly growing tumors among studies conducted in Asia -- sorry, in recent studies with diverse liver disease etiologies reported more indolent growth among patients with nonviral liver disease.
What is "nonviral liver disease"?
A. Nonviral means not related to Hepatitis B or Hepatitis C.
Q. And so HCCs that are not related to

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Hep A or -- sorry. Scratch that.
HCCs that are not related to Hep B or Hep C typically grow slower, correct?
A. Yes. I'd say so.
Q. And the study authors say that's particularly important in the western world.
That's here in the United States right, the "western world"?
A. Yes.
Q. Where -- where HCC is increasingly related to nonviral etiologies such as NASH and alcohol-related cirrhosis.
And so is this saying that HCC that is related to NASH is typically slow-growing?
A. Yes. That's --
MS. ROSE: Object to the form.
THE WITNESS: It's fair to say that HCC in NASH is typically more slow-growing than what you would observe in viral hepatitis-related HCC.
BY MR. VAUGHN:
Q. And it's your opinion that Mr. Roberts' HCC is related to NASH, correct?
A. Yes. My opinion is that HCC in Mr. Roberts' case -- well, it's -- it's related

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to -- again, there's multiple risk factors, but I think the primary one is his MASH-related cirrhosis. Yeah.
So I mean, but -- but I think we were highlighting his -- he's more likely to have a slow-growing tumor. So -- so there's less reason to assume that he would have extremely rapid growth.
He's more likely to be on the side of the distribution of a slow-growing tumor, which, again, is modeled in that table I showed you. So if we took, you know, the assumption of slow growth, which is 5.3 months, then we absolutely would have expected that he -- you know, he would have had, you know, lesions in the liver at that time.
So I think that's, once again, consistent with what I'm -- what I'm modeling here.
Q. And so if we go with the slow growth, which would be what you would expect with HCC from someone with NASH, when the radiology report from 4/18/16 was done, he should have nearly a 2-centimeter tumor at that time, right?

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MS. ROSE: Object to the form.
THE WITNESS: So look, these are not guaranteed -- guarantees. There's variation within every etiology of liver disease. It's not like every single patient with NASH-related cirrhosis will have a growth rate of 5.3 centimeters. There's inherent variability based on myriad factors.
So, you know, all this is communicating is that it's more likely than not that he already had hepatocellular carcinoma present in the liver when he was first exposed to NDMA.
There's going to be variation in what the actual size of the lesions might have been. There's -- and, of course, there's error introduced by the assumption of a sphere.
So this is not a perfect prediction. But in the plausible ranges of where most patients fit -- and in particular patients with NASH or MASH-related cirrhosis, as you've highlighted, where the tumors grow more

slowly, he's almost guaranteed to have already had hepatocellular carcinoma when he was -- when he was first exposed to NDMA-contaminated Valsartan.

MR. VAUGHN: I pass the witness.

MS. ROSE: Can we take a break just for a second?

THE VIDEOGRAPHER: Off the record, 5:49.

(Whereupon, a break was taken.)

THE VIDEOGRAPHER: We are back on the record at 6:06.

MS. ROSE: Dr. Mahmud, I want to thank you so much for taking time out of your schedule for this deposition today.

I don't have any questions for you at this time, so I think the deposition is concluded.

THE WITNESS: Okay.

THE VIDEOGRAPHER: That concludes today's deposition. The time is 6:07.

(The witness is excused.)

(Deposition of Nadim Mahmud, M.D., concluded at 6:07 p.m. EDT.)

C E R T I F I C A T E

I, SUZANNE J. STOTZ, a Certified Court Reporter, Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the State of New Jersey, do hereby certify that the foregoing is a true and accurate transcript of the stenographic above-captioned matter.

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